PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/70

A1

(11) International Publication Number: **WO 99/63972**

(43) International Publication Date: 16 December 1999 (16.12.99)

(21) International Application Number: PCT/US99/12772

(22) International Filing Date: 8 June 1999 (08.06.99)

(30) Priority Data:

09/095,616	10 June 1998 (10.06.98)	US
09/095,246	10 June 1998 (10.06.98)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application

US Not furnished (CIP)
Filed on Not furnished

(71) Applicant *(for all designated States except US)*: DELSYS PHARMACEUTICAL CORPORATION [US/US]; Suite 305, 5 Vaughn Drive, Princeton, NJ 08540 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHEN, Jen-Chi [-/US]; 80 Annamarie Avenue, Morrisville, PA 19067 (US). CHRAI, Suggy, S. [-/US]; 16 Bodine Drive, Cranbury, NJ 08512 (US). DESAI, Nitin, Vithalbhai [-/US]; 7 Amhert Way, Princeton Junction, NJ 08550 (US). HAMMER, Lawrence, Harrison [-/US]; 507 Aspen Drive, Plainsboro, NJ 08536 (US). KELLER, David [-/US]; 353 Cambridge Lane, Newton, PA 18940 (US). KUMAR, Nalin [-/US]; 413 Longstone Drive, Cherry Hill, NJ 08003 (US). LAL, Prince [-/US]; 304 Philmar Avenue, Cherry Hill, NJ 08003 (US). LEVINE, Aaron, William [-/US]; 6 Springwood Drive, Lawrenceville, NJ 08648 (US). MURARI, Ramaswamy [-/US]; 39 Wesley Road, Hillsborough, NJ 08876 (US). O'MARA, Kerry, Dennis [-/US]; 7 Lynnbrook Drive, Hopewell Township, Mercer, NJ 08530 (US). POLINIAK, Eugene, Samuel [-/US]; 13 Glover Lane, Willingboro, NJ 08046 (US). RIVENBURG, Howard, Christopher [-/US]; 16 Fontaine Court, Princeton, NJ 08540 (US). ROACH, William, Ronald [-/US]; 70 Hickory Court, Rocky Hill, NJ 08853 (US). ROSATI, Dominic, Stephen [-/US]; 44 Amsterdam Road, Hamilton, NJ 08620 (US). SINGH, Bawa [-/US]; 12 Whythe Drive, Voorhees, NJ 08043 (US). SOUTHGATE, Peter, David [-/US]; 958 Ridge Road, Monmouth Junction, NJ 08852 (US). SUN, Hoi, Cheong [-/US]; 3402 Wildwood Court, Monmouth Junction, NJ 08852 (US). ZANZUCCHI, Peter, John [-/US]; 13 Jill Drive, Lawrenceville, NJ 08648 (US).

(74) Agent: BREYER, Wayne, S.; DeMont & Breyer, LLC, 35 Malus Lane, Middletown, NJ 07748 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

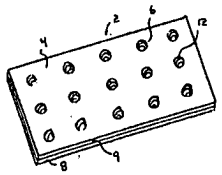
Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL PRODUCT AND METHODS AND APPARATUS FOR MAKING SAME

p. 46 Base Substrate



(57) Abstract

The present invention provides a product (1) that includes a pharmaceutical unit dosage or diagnostic form (6) that includes at least one active ingredient that is present in an amount that advantageously does not vary by more than about five percent from a predetermined target amount. In one embodiment, the unit form comprises a substrate (8), a deposit (14) that is disposed on the substrate and a cover layer (9) that overlies the deposit and is joined to the substrate by a bond that encircles that deposit, thereby encapsulating it between the substrate and cover substrates. The deposit comprises a powder, at least some of which includes the at least one active ingredient. The unit form is created via a dry powder deposition apparatus that electrostatically deposits the powder on the substrate utilizing an electrostatic chuck and charged powder delivery apparatus.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PHARMACEUTICAL PRODUCT AND METHODS AND APPARATUS FOR MAKING SAME

Cross Reference to Related Cases

The following U.S. patents are of interest: Pat. No. 5,669,973 issued 23-Sep-97 to Pletcher et al., *APPARATUS FOR ELECTROSTATICALLY DEPOSITING AND RETAINING MATERIALS UPON A SUBSTRATE*; Pat. No. 5,714,007 issued 03-Feb-98 to Pletcher et al., *APPARATUS FOR ELECTROSTATICALLY DEPOSITING A MEDICAMENT POWDER UPON PREDEFINED REGIONS OF A SUBSTRATE*; Pat. No. 5,788,814 issued 04-Aug-98 to Sun, *CHUCKS AND METHODS FOR POSITIONING MULTIPLE OBJECTS ON A SUBSTRATE*; Pat. No. 5,753,302 issued 19-May-98 to Sun et al., *ACOUSTIC DISPENSER*; Pat. No. 5,846,595 issued 08-Dec-98 to Sun et al., *ELECTROSTATIC CHUCKS*; Pat. No. 5,858,814 issued 12-Jan-99 to Sun et al., *ELECTROSTATIC CHUCKS*; Pat. No. 5,871,010 issued 16-Feb-99 to Datta et al., *INHALER APPARATUS WITH MODIFIED SURFACES FOR ENHANCED RELEASE OF DRY POWDERS.*

The following U.S. patent applications are of interest: S.N. 08/659,501 filed 06-Jun-1996 by Pletcher et al., *METHOD AND APPARATUS FOR ELECTROSTATICALLY DEPOSITING A MEDICAMENT POWDER UPON PREDEFINED REGIONS OF A SUBSTRATE*; S.N. 08/733,525 filed 18-Oct-96 by Pletcher et al., *METHOD AND APPARATUS FOR ELECTROSTATICALLY DEPOSITING A MEDICAMENT POWDER UPON PREDEFINED REGIONS OF A SUBSTRATE*; S.N. 08/956,348 filed 23-Oct-97 by Loewy et al., *DEPOSITED REAGENTS FOR CHEMICAL PROCESSES*; S.N. 08/956,737 filed 23-Oct-97 by Loewy et al., *SOLID SUPPORT WITH ATTACHED MOLECULES*; S.N. 09/026,303 filed 19-Feb-98 by Sun, *BEAD TRANSPORTER CHUCKS USING REPULSIVE FIELD GUIDANCE*; S.N. 09/047,631 by Sun, *BEAD MANIPULATING CHUCKS WITH BEAD SIZE SELECTOR*; S.N. 08/083,487 filed 22-May-98 by Sun, *FOCUSED ACOUSTIC BEAD CHARGER/DISPENSER FOR BEAD MANIPULATING CHUCKS*; S.N. 09/095,425 filed 10-Jun-98 by Sun et al., *AC WAVEFORMS BIASING FOR BEAD MANIPULATING CHUCKS*, and S.N. 09/095,321 filed 10-Jun-98 by Sun et al., *APPARATUS FOR CLAMPING A PLANAR SUBSTRATE*; S.N. 09/095,616 filed 10-Jun-98 by Chrai et al., *PHARMACEUTICAL PRODUCT AND METHOD OF MAKING*; and S.N. 09/095,246 filed 10-Jun-98 by Desai et al., *DRY POWDER DEPOSITION APPARATUS.*

Field of the Invention

The present invention relates generally to unit dosage or unit diagnostic forms and an apparatus and method for making such unit forms.

Background of the Invention

In the pharmaceutical industry, pharmaceutical products including diagnostic products comprise a container (*e.g.*, a bottle, a blister pack or other packaging) containing a plurality of "unit dosage forms" or "unit diagnostic forms." Each of such unit forms contains a pharmaceutically- or biologically-active ingredient or ingredients and inert or inactive ingredient(s).

The pharmaceutically-active ingredient typically forms a drug. The diagnostic form may comprise a reagent or the like for use in diagnostic tests, and may be part of a set which includes several different reagents or active ingredients. Moreover, the diagnostic form may comprise an antibody, an antigen, or labeled forms thereof and the like.

A pharmaceutically- or biologically-active ingredient for use in a unit form may be supplied as a powder comprising a plurality of active-ingredient particles. Such active-ingredient particles are combined with inert or inactive ingredient particles to form a plurality of "major particles." The major particles are quite small, with dimensions on the order of microns. Such major particles are typically combined with one another to create the final unit dosage or diagnostic form (*e.g.*, tablet, caplet, test strip, capsule, *etc.*).

There may be significant variation in the amount of pharmaceutically- or biologically-active ingredient in one major particle and the next. Since a large number of major particles are required to create a final unit form, the aforedescribed particle-to-particle variation may result in a substantial variation in the amount of active ingredient between one unit form and the next. Thus, any given final form may contain substantially more or less than a desired amount of active ingredients.

Destructive analytical screening procedures are conventionally performed to assess the amount of active ingredient(s) in final unit forms. Since such procedures destroy the unit forms, a statistical sampling is performed whereby a relatively small number of forms per batch are actually sampled and tested. Such screening procedures disadvantageously provide no assurance that all forms in a given batch contain a desired amount of the

pharmaceutically- or biologically-active ingredients. In fact, such statistical methods practically "guarantee" that a statistically determinable percentage of the forms in each batch will be out of specification.

As such, the art would benefit from a method and apparatus that provides improved control over the active-ingredient content of unit dosage and diagnostic forms.

Summary of the Invention

In one embodiment, the present invention provides a product comprising a plurality of pharmaceutical unit dosage forms or unit diagnostic forms (collectively, "unit forms"). Each form includes at least one active ingredient that is present in an amount that advantageously does not vary by more than about five percent from a predetermined target amount.

In one embodiment, the unit form comprises a substrate, an active ingredient deposited thereon, and a cover layer that covers the active ingredient and is joined (*e.g.*, via welding, adhesives, *etc.*) to the substrate in the proximity of the active ingredient.

In the illustrated embodiments, the product is made via a dry deposition apparatus that deposits powder/grains on the substrate. In one embodiment, the apparatus comprises an electrostatic chuck, a charged powder delivery apparatus, and an optical detection system. The substrate is engaged to the electrostatic chuck for the dry deposition of powder. The chuck has at least one collection zone at which a powder-attracting electrical field is developed. The charged powder-delivery apparatus directs charged powder for electrostatic deposition to the substrate at the collection zone(s). The optical detection system quantifies the amount of powder deposited.

In some embodiments, the dry deposition apparatus also includes an electronic processor for controlling depositions responsive to sensor inputs. Such sensor inputs advantageously include one or more deposition sensors that are disposed on or adjacent to the electrostatic chuck and that provide data pertaining to the amount of powder deposited. Responsive to sensor data, the electronic processor adjusts deposition parameters, as necessary. Controllable parameters include powder flux through the powder-delivery apparatus and applied voltage at the collection zone(s).

In still other embodiments, the present dry deposition apparatus advantageously includes a variety of other elements that are described in detail later in this Specification.

Brief Description of the Drawings

FIG. 1 depicts an isometric view of a product comprising a strip package containing a plurality of unit forms in accordance with an illustrated embodiment of the present invention.

FIG. 2 depicts a cover layer of a strip package partially separated from a substrate.

FIG. 3 depicts a side view of an illustrative unit form in accordance with the present teachings.

FIG. 4 depicts a top view of the illustrative unit form of FIG. 3.

FIG. 5 depicts a packaging container for storing the product of FIG. 1.

FIG. 6 is a figurative depiction of an apparatus for making the present product.

FIG. 7 depicts a top view of a robotic platform in accordance with an embodiment of the present invention.

FIG. 8 depicts a side elevation of the robotic platform of FIG. 7.

FIG. 9 figuratively depicts, via side-elevation, an embodiment of a robotically-operated receiver and an electrostatic chuck for carrying a substrate upon which the unit forms are deposited.

FIG. 10 depicts a plan view of a first surface of an illustrative electrostatic chuck.

FIG. 11 depicts a plan view of a second surface of an illustrative electrostatic chuck.

FIGS. 12a - 12c depict side cross-sectional views of embodiments of the electrostatic chuck of FIGS. 10 and 11 near a collection zone.

FIG. 13 depicts a front elevation of the receiver and electrostatic chuck shown in FIG. 9, and further depicts an illustrative arrangement for electrically connecting the electrostatic chuck to a circuit board in the receiver.

FIG. 14 depicts a side view of an illustrative lower pin assembly useful for connecting the electrostatic chuck to a circuit board in the receiver.

FIG. 15 depicts a gasket disposed between the electrostatic chuck and the receiver.

FIG. 16 depicts a top view of the illustrative lower pin assembly of FIG. 14.

FIG. 17 depicts the underside the illustrative receiver with the electrostatic chuck adhered thereto.

FIG. 18 depicts the underside the illustrative receiver without the electrostatic chuck.

FIG. 19 depicts a receiver platform for supporting components that comprise the receiver.

FIG. 20 depicts the receiver platform supporting several electronic components.

FIGS. 21 & 22 depict further details of the receiver and the manner in which it is engaged to the robotic transport element.

FIG. 23 depicts a lamination support block for laminating the substrate and cover layer together.

FIG. 24 depicts a deposition engine for electrostatically depositing powder on a substrate.

FIGS. 25 and **26** depict a rotatable baffle for use in dispersing the powder at a powder deposition station.

FIG. 27 depicts an illustrative powder trap for capturing powder that does not deposit.

FIGS. 28 and **29** depict an alternative embodiment of a receiver, electrostatic chuck and deposition station in accordance with the present teachings.

FIG. 30 depicts a first alternative embodiment of a powder feed apparatus.

FIG. 31 depicts a second alternative embodiment of a powder feed apparatus.

FIG. 32 depicts powder measurement via a diffuse reflection methodology.

FIG. 33 depicts powder measurement via an optical profilometry methodology.

FIG. 34 depicts a first measurement apparatus capable of both diffuse reflection and optical profilometry based-measurements.

FIG. 35 depicts the operation of the apparatus of FIG. 34 operating according to diffuse reflection methodology.

FIG. 36 depicts the operation of the apparatus of FIG. 34 operating according to optical profilometry methodology.

FIG. 37 depicts a second measurement apparatus capable of both diffuse reflection and optical profilometry based-measurements.

FIG. 38 depicts a plot that was developed based on data obtained using diffuse reflection measurements.

FIG. 39 depicts a sealing head that is positioned over a substrate and a cover layer in preparation for laminating them together.

FIG. 40 depicts a first illustrative equivalent circuit diagram for AC-biased charge and deposition sensing for a collection zone.

FIG. 41 depicts plots of waveforms of voltages measured at a floating pad electrode and a collection zone.

FIG. 42 depicts a second illustrative equivalent circuit diagram for AC-biased charge and deposition sensing for a collection zone.

FIGS. 43a-43c depict an illustrative method based on blow-fill-seal technology for fabricating a final dosage form.

FIG. 43d depicts an illustrative final dosage form produced from the method of FIGS. 43a-43c.

FIGS. 44a-44b depict a further illustrative method for fabricating a final dosage form.

FIG. 44c depicts an illustrative final dosage form produced from the method depicted in FIGS. 44a-44b.

FIG. 45a depicts an additional method for fabricating a final dosage form.

FIG. 45b depicts an illustrative final dosage form produced from the method depicted in FIG. 45a.

FIG. 46 depicts an illustrative embodiment of a final dosage form suitable for providing timed release of a plurality of unit forms contained within the final dosage form.

FIG. 47 depicts a further illustrative embodiment of a final dosage form suitable for providing timed release of a plurality of unit forms contained within the final dosage form.

FIG. 48 depicts a bi-layer substrate.

FIG. 49 depicts a method for making the bi-layer substrate of FIG. 48.

Detailed Description

The following terms shall have the respective meanings set forth below for the purposes of this description and the appended claims.

Dielectric or non-conductive refers to materials that are non-conductive to a degree that distinguishes them from conductive materials such as copper and the like. The degree of non-conductance can vary considerably with context.

Dry deposited refers to depositing a material without using a liquid vehicle.

Effective amount means an amount effective to (1) reduce, ameliorate or eliminate

one or more symptoms of a subject disease; (2) induce a pharmacological change relevant to treating a subject disease; or (3) prevent or lessen the frequency of occurrence of a subject disease, or symptoms thereof.

Electro-attractive dry deposition refers to methods that use an electromagnetic field, or an electrostatically-charged surface to dry deposit charged powder.

Grains are aggregates of either molecules or particles, such as the particles comprising a powder, or polymer structure that can be referred to as "beads." Beads can be coated, have adsorbed molecules, have entrapped molecules, or otherwise carry other substances. The particles or molecules of a powder have an average diameter that is typically at least about 1 nanometer (nm), and more typically in the range of about 100 nm to about 500 nm. Grains have a diameter that is in the range of about 100 nm to about 5 millimeters (mm), and more typically at least about 500 nm or 800 nm in average diameter.

Planar substrate denotes a substrate having two major dimensions, such as a tape or a sheet. While in some embodiments, planar substrates are flat, they need not be.

Unit form (pharmaceutical dosage or diagnostic) includes one or more discrete active ingredients (whether or not on a separate substrate and whether or not the substrate is edible) that can be used as a dosage for pharmaceutical purposes or as an element(s) for diagnostic purposes, whether or not encapsulated, whether or not capable of being packaged or otherwise available for end use as a unit.

Product and Unit Form

FIG. 1 depicts a product **1** in accordance with an illustrative embodiment of the present invention. Product **1** comprises a package **2** that is realized as a strip **4** having an array of unit dosage forms **6**. Strip **4** comprises a substrate **8** and a cover layer **9**.

Substrate **8** and cover layer **9** each comprise a substantially planar, flexible film or sheet. In some embodiments, one of either substrate **8** or cover layer **9** includes an array of semi-spherical bubbles, concavities, blisters or depressions (hereinafter "bubbles") **12** that are advantageously arranged in columns and rows. In the illustrative package depicted in FIG. 1, cover layer **9** comprises a three-by-five array of such bubbles **12**, although more or fewer bubbles may suitably be provided. Substrate **8** and cover layer **9** are advantageously formed to have a thickness of about 0.001 inches (0.0254 mm) and typically comprise a thermoplastic material. Materials suitable for use as substrate **8** and/or cover layer **9** include,

without limitation, polyvinylacetate, hydroxypropylmethylcellulose and polyethylene oxide films. Polyvinylacetate films suitable for use as the substrate and/or cover layer are commercially available from Polymer Films, Inc. of West Haven, CT; Chris Craft of Gary, IN; Aquafilm of Winston-Salem, NC; Idroplast S.p.A. of Montecatini Terme (PT), Italy; AICello Chemical Co., Ltd. of Toyohashi; Japan; and Soltec of Paris, France.

As depicted in FIG. 2 (showing cover layer 9 partially "peeled" back from substrate 8) and FIG. 3, a deposit of a dry active ingredient **14**, in the form of powder(s)/grains (hereinafter, "powder,") is disposed between substrate **8** and cover layer **9** within a bubble **12**. In some embodiments, active ingredient **14** is a pharmaceutical product, such as a drug; in other embodiments, active ingredient **14** is a diagnostic product that is useful for biological diagnostic laboratory or medical related purposes. The method and means by which active ingredient **14** is deposited on substrate **8** is described later in this specification. As used herein, the term "powder" signifies a single (*i.e.*, one type of) powder as well as multiple (*i.e.*, different types of) powders.

As depicted via a cross-sectional view in FIG. 3 and plan view in FIG. 4 (each showing only a single bubble **12**), substrate **8** and cover layer **9** are attached to one another via bonds or welds **7** that are near to and encircle bubble **12**. Bonding can be effected, for example, via heat or ultrasonic welding or via suitable adhesives. Unit form **6** comprises a deposit of active ingredient **14**, bubble **12**, and a region of substrate **8** within bonds **7**.

As depicted in FIG. 5, strips **4** containing unit forms **6** can be provided, for example, in a box **16** or like packaging container, for the convenience of a user.

Unit dosage forms **6** in accordance with the present teachings can be used to form a variety of final dosage forms. Illustrative final dosage forms incorporating one or more unit dosage forms **6** are described later in this specification after various embodiments of an apparatus for making unit dosage forms **6** are described.

Apparatus for Making the Present Product

FIG. 6 depicts, conceptually, the elements of an apparatus **100** suitable for making the present product. Apparatus **100** comprises platform **101** wherein the unit forms in accordance with the present invention are created. Platform **101** is advantageously adapted for robotic operation, as depicted in the illustrative embodiments. In other embodiments, however, platform **101** is not robotic. In such other embodiments, platform **101** includes, for

example, manually-operated mechanisms (*e.g.*, gantry and crane) for retrieval and transit of substrates, *etc.* Platform **101** creates such unit forms via a variety of operations, chief of which is the electrostatic deposition of dry powder on defined discrete regions of a substrate. Additional operations include some or all of the following: materials handling, alignment, dose measurement and lamination.

Electrostatically-charged powder is delivered to robotic platform **101** via powder feed apparatus **801.** Processor **401** and controller **403** control various electronic functions of apparatus **100**, such as, for example, the application of voltage for the electrostatic deposition operation, the operation of powder feed apparatus **801**, the operation of robots that are advantageously in conjunction with platform **101**, and dose measurement operations. Memory **405** is accessible to processor **401** and controller **403.**

In some embodiments, platform **101** and/or powder feed apparatus **801** are isolated from the ambient environment by an environmental enclosure. In such environments, environmental controller **901** provides temperature, pressure and humidity control for robotic platform **101** and powder feed apparatus **801**.

A detailed description of the aforementioned elements of apparatus **100** is provided below.

The Platform and the Operation Thereof

FIGS. 7 and 8 depict a top view and a front elevational view, respectively, of illustrative platform **101**. Four supports **104** are disposed one at each corner of platform **101**. Supports **104** elevate support bench **110** and various structures associated with platform **101** above a table or like surface. Additionally, supports **104** advantageously provide a frame or superstructure for optional side-mounted barriers **106**, depicted in FIG. 7. Side mounted barriers **106** may be comprised of glass, polycarbonate or acrylic panes and the like. The side-mounted barriers, in conjunction with a top barrier (not shown) and support bench **110** define an environmental enclosure or chamber **102** that isolates the region therein from the ambient environment under air or inert gas.

Support bench **110** comprises five processing stations that perform various operations advantageously used to produce the present product. Briefly, those processing stations include: input/output station **120**, advantageously comprising three substations **120A**, **120B** and **120C**, for storing substrates and cover layers; alignment station **130** for

assuring that the substrate and cover layer are properly aligned to their transport mechanism; deposition station **150** where powder are deposited on the substrate; dose measurement station **140** for measuring the amount of powder that is deposited on the substrate; and lamination station **160** where the cover layer is laminated to the substrate.

In the illustrated embodiment, platform **101** is adapted for robotic operation by way of first robotic transport element **170** and second robotic transport element **180**. A receiver **172** is attached to first robotic transport element **170**. Receiver **172** is operable, as discussed in further detail later in this specification, to retrieve at least the substrate from substation **120C** and to move it to at least some of the various operational stations **130-160** for processing. A "bonding" head **182** is attached to second robotic transport element **180**. Bonding head **182** is operable, as discussed in further detail later in this specification, to join/seal the substrate and cover layer to one another.

Robotic transport elements **170** and **180** are movable (*e.g.*, to access different processing stations) along first rails **190** that provide guides for motion in one direction (*e.g.*, along the x-axis). Additional rails (not shown) movably mounted on first rails **190** provide guides/support for motion in a direction orthogonal (*e.g.*, the y-axis) to first rails **190**, to provide x-y motion. Drive means (not shown), such as x-y stepper motors, move robotic transport elements **170** and **180** along the rails. First and second robotic transport elements **170** and **180** have telescoping components under servo control (not shown) that provide movement along the z axis (*i.e.*, normal to the x-y plane). Such z-axis movement allows receiver **172** or bonding head **182** to move "downwardly" toward a processing station to facilitate an operation, and "upwardly" away from a processing station after the operation is completed. Robotic transport elements **170** and **180** advantageously include θ control components under servo control (not shown) that allow receiver **172** and bonding head **182** to be rotated in the x-y plane as may facilitate operations at a processing station. Compressed dry air or other gas is suitably provided, such as at a flow rate of 8 SCFM at 80 psi, to operate the robotic transport elements. Robotic transport elements **170** and **180** can be based, for example, on a Yaskawa Robot World Linear Motor Robot available from Yaskawa Electric Company of Japan.

The following disclosure provides a description of embodiments of various elements and features of apparatus 100. To provide perspective for such disclosure, a summary of at least one embodiment of the operation of apparatus 100 is first presented.

In operation, first robotic transport element **170** moves receiver **172** and an engaged electrostatic chuck **202** (used for powder deposition, *see*, FIGS. 9-11, *etc.*) to input/output station **120**. At station **120**, the electrostatic chuck engages substrate **80** and, in some embodiments, also engages a frame **81** that is joined to the substrate. In one embodiment, robotic transport element **170** then moves the engaged receiver **172**, electrostatic chuck **202**, substrate **80** and frame **81** to alignment station **130**. At the alignment station, frame **81** is re-aligned to electrostatic chuck **202** via various alignment mechanisms, thereby improving the accuracy and consistency of alignment of substrate **80** with electrostatic chuck **202**.

Robotic transport element **170** then moves engaged receiver **172**, electrostatic chuck **202**, substrate **80** and frame **81** to dose measurement station **140**. After aligning with a measurement apparatus at station **140**, substrate **80** is scanned via a measurement device and distances from a reference point to substrate **80** at each of a plurality of "collection zones" **CZ** (*see* FIG. 10) are calculated and recorded to provide baseline data.

Robotic transport element **170** then moves engaged receiver **172**, electrostatic chuck **202**, frame **81** and "virgin" substrate **80** to deposition station **150**. At deposition station **150**, the powder deposition engine (*see* FIGS. 23 - 29) is turned on and powder is electro-deposited at collection zones **CZ**.

At the completion of the powder-deposition operation, robotic transport element **170** returns substrate **80**, with its complement of deposited powder, to dose measurement station **150**. At station **150**, the measurement device again scans substrate **80** to determine the distance between the reference point to the surface of the "deposit" of powder accumulated at each collection zone **CZ**. From such distances, and the previously obtained baseline data, the amount (*e.g.*, volume) of powder deposited at each collection zone is calculated. If the calculated amount is outside a desired range of a predetermined target amount, such information is displayed. An operator can then suitably adjust operating parameters to bring the process back into specification. In another embodiment, automatic feed back is provided to automatically adjust the process, as required. The "out-of-spec" unit forms may be discarded.

Second robotic transport element **180** picks up cover layer **90** and frame **91** from input/output station **120** and delivers them to lamination station **160**. After measurements are completed at dose measurement station **150**, first robotic transport element **170** delivers substrate **80** with its complement of powder to lamination station **160**. Substrate **80** is

placed, via first robotic transport element **170**, on cover layer **90** such that the deposits of powder are properly aligned within the perimeter of the blisters or bubbles in the cover layer.

After first robotic transport element **170** moves away, second robotic transport element **180** returns and, by the operation of bonding head **182**, welds the substrate and cover layer together, forming a plurality of unit forms on a strip (*see*, FIG. 1). In an automated system, the unit forms may be automatically transferred to a packaging station wherein out-of-specification unit forms are screened out and in-spec unit forms are appropriately packaged.

The present method and apparatus provide a product containing a plurality of pharmaceutical or diagnostic unit forms, each comprising at least one pharmaceutically or diagnostic active ingredient that advantageously does not vary from a predetermined target amount by more than 5%.

Having provided an overview of an embodiment of the present invention, further detailed description of illustrative embodiments of various elements and features of apparatus **100** and the operation thereof are now provided.

The Receiver, Electrostatic Chuck and Substrate Assembly

In accordance with the present invention, powder comprising an active ingredient is electrostatically deposited at discrete locations on substrate **80** at deposition station **150**. In the illustrated embodiments, accomplishing such deposition requires that, among other things, substrate **80** is transported to deposition station **150** from some other location, and that an electrostatic charge is developed that causes the powder to electrostatically deposit on substrate **80**. Such transport and charging operations are facilitated, at least in part, via receiver **172** and electrostatic chuck **202**. Before providing a detailed description of such elements, an overview of the cooperative relation between receiver **172**, electrostatic chuck **202** and substrate **80** is provided below in conjunction with FIG. 9.

FIG. 9 is a simplified representation that depicts receiver **172** engaged to electrostatic chuck **202**. Illustrative receiver **172** comprises electronics housing **1610**, vacuum manifold housing **1620**, and gasket **1630**, interrelated as shown. Electrostatic chuck **202** is engaged to receiver **172** against gasket **1630**. Substrate **80** (not shown in FIG. 9) is releaseably secured to electrostatic chuck **202**. Electronics housing **1610** includes circuitry, described in more detail later in this specification, for controlling the operation of electrostatic chuck **202**.

Reduced pressure (*e.g.*, partial vacuum) is applied to passageways **1622** of vacuum manifold housing **1620** via inlet fitting **1621** and a passageway outlet (not shown). Passageways **1622** convey reduced pressure to "through holes" in electrostatic chuck **202** (not shown in FIG. 9; *see* through holes **ECH** in FIGS. 10 and 11). Substrate **80** is in turn exposed to such reduced pressure via openings in gasket **1630** (not shown in FIG. 9, *see* slots 1631 in FIG. 15). The reduced pressure releaseably secures the substrate to electrostatic chuck **202**. Further detailed description of receiver **172**, electrostatic chuck **202** and substrate **80** and cover layer **90** is provided below.

In the illustrated embodiments, the substrate and cover layer are stored at input/output substations **120A**, **120B** and **120C**, and are advantageously mounted on frames. More particularly, substrates **80** are advantageously mounted on frames **81** forming substrate assemblies **82**, and cover layers **90** are advantageously mounted on frames **91** forming cover assemblies **92**. As depicted in FIGS. 2 and 3, substrate **80** is a planar film and cover layer **90** is a substantially planar, flexible film having an array of semi-spherical bubbles or blisters that are advantageously arranged in columns and rows.

In the illustrative embodiment depicted in FIG. 7, first input/output substation **120A** contains substrate assemblies **82**, second input/output substation **120B** contains cover assemblies **92**, and third input/output substation **120C** contains interlocked frames **81** and **91** containing substrates **80** and cover layers **90** after bonding/lamination.

As described further below, frames **81** and **91** advantageously aid in aligning the substrates **80**, **90** to various elements of apparatus **100**. The frames are made of a suitably strong material that is preferably "light weight," such as, for example, aluminum. Frames having a rectangular shape with the shorter sides measuring about 200 mm and the longer sides measuring about 300 mm, and all sides having a thickness of about 12.7 mm have found to be suitable for use in conjunction with the present invention.

FIG. 10 depicts a view of first surface **204** of electrostatic chuck **202**. Electrostatic chuck **202** comprises a layer **203** of dielectric material such as, for example, Kapton® brand polyimide film commercially available from Dupont de Nemours, Wilmington, DE. The electrostatic chuck has a thickness of about 0.01 inches (0.25 mm), and, as such, is relatively flexible. Illustrative electrostatic chuck **202** has "through holes" **ECH** implemented as slots that are disposed at its periphery. Other suitable configurations for electrostatic chuck "through holes" are illustrated in U.S. Pat. App. No. 09/095,321. First surface **204** further

includes a plurality of powder collection zones **CZ**. In illustrative electrostatic chuck **202**, collection zones **CZ** are advantageously organized in eight columns $207_{C1 - C8}$ of twelve collection zones each for a total of ninety-six collection zones **CZ**. As will be described further later in this specification, each collection zone **CZ** corresponds to a powder deposition location on the substrate (*see* substrate **8** in FIG. 1). Collection zones **CZ** are formed within electrostatic chuck **202** by an arrangement of dielectric and conductive regions, several embodiments of which are described later in this specification in conjunction with FIGS. 12a - 12c.

FIG. 11 depicts a view of second surface **206** of electrostatic chuck **202**. As depicted in more detail in FIGS. 12a - 12c, collection zones **CZ** are formed via electrical contact pads **208**. Such electrical contact pads **208** provide contact points for connection to a controlled voltage source. Electrical contact pads **208** are electrically connected to selected other electrical contact pads via address electrodes **210**.

By virtue of discrete electrical contact pads **208**, and address electrodes **210** that electrically connect select groupings of such contact pads (*e.g.*, the pads **208** within a given column $207_{C1 - C8}$ of illustrative chuck **202** of FIG. 11 define an illustrative grouping), a first voltage can be applied to contact pads **208** in column 207_{C1}, while a second voltage different from the first voltage can be applied to contact pads **208** in second column 207_{C2}, and so forth varying the voltage applied to contact pads **208** on a column-by-column basis as desired. It will be understood that the application of such different voltages to such different columns results in depositing a different amount of powder at collection zones **CZ** in each of such columns. It will be appreciated that in other embodiments, address electrodes are arranged differently thereby creating electrical interconnects between differently arranged groupings of contact pads **208**. For the layout of contact pads **208** and address electrodes **210** depicted in FIG. 11, voltage need only be applied to a single contact pad **208** within a given column **203** for substantially the same electrostatic charge to be developed at each contact pad **208** within that column.

FIGS. 12a -12c depict several illustrative embodiments of structural arrangements suitable for forming collection zones **CZ** within an electrostatic chuck, such as electrostatic chuck **202**. For clarity of illustration, the structure associated with only a single collection zone **CZ** of an electrostatic chuck is depicted in FIGS. 12a - 12c.

In a first embodiment depicted in FIG. 12a, a conductive material **305** is disposed through layer **303** of dielectric at each region designated to be a collection zone **CZ**. The conductive material overlays a portion of first surface **304** and second surface **306** of the electrostatic chuck. The portion of conductive material **305** overlying first surface **304** comprises a powder-attracting electrode **307A**, while the portion of conductive material **305** overlying the second surface **306** comprises electrical contact pad **308A** (equivalent to the electrical contact pads previously described, such as contact pad **208** depicted in FIG. 11). A shield electrode **312** (also termed a "ground electrode" based on a preferred bias) is disposed within layer **303**.

Applying a voltage to electrical contact pad **308A** generates an electrostatic field at powder-attracting electrode **307A** at collection zone **CZ**. As described later in this specification, the electrostatic field attracts charged powder to the substrate (*e.g.*, substrate **380**). Additionally, the electrostatic field aids in holding substrate **380** flat against first surface **304** of the electrostatic chuck. The reduced pressure that is developed in vacuum manifold housing **1620** (*see* FIG. 9) to which substrate **380** is exposed also assists in adhering substrate **380** to the electrostatic chuck. Tight adherence of the substrate **380** to the electrostatic chuck increases the reliability of powder deposition at the collection zones.

FIG. 12b depicts a second illustrative embodiment where through holes **ECH** are formed at electrical contact pad **308B** and powder-attracting electrodes **307B**. FIG. 12c depicts a third illustrative embodiment wherein an additional layer **314** of dielectric material separates powder-attracting electrode **307C** from base substrate **380**. Electrical contact-pad **308C** overlays second surface **306** of layer **303**.

The electrostatic chuck provided by the configuration depicted in FIG. 12c can be termed a "Pad Indent Chuck" which is useful, for example for powder depositions of less than about 2 mg, preferably less than about 100 μg, per collection zone **CZ** (assuming, for example, a collection zone having a diameter within the range of 3-6 mm diameter). The electrostatic chuck provided by the configuration depicted in FIG. 12a can be termed a "Pad Forward Chuck" which is useful, for example, for powder depositions of more than about 20 μg per collection zone **CZ** (again assuming a collection zone of about 3-6 mm diameter). The Pad Forward Chuck is more useful than the Pad Indent Chuck for higher dose depositions.

It should be clear from earlier description that a voltage source must be electrically connected to the powder-attracting electrodes (hereinafter generically identified by the call-

out "307"). An illustrative arrangement for providing such connection is depicted in FIG. 13, which depicts receiver **172** engaged to electrostatic chuck **202** as in FIG. 9, but viewed from the perspective indicated by the arrows identified as "13" in FIG. 9.

Electrical connection to powder-attracting electrodes **307** is effected via coupled pins **1623**. Each coupled pin **1623** comprises a pin **1627** and a lower pin assembly **1624**. Pin **1627** is advantageously a standard circuit board pin. As depicted via side view in FIG. 14, lower pin assembly **1624** has a slot **1625** for receiving pin **1627** (not shown). Pins **1627** couple with slots (not shown) on pin connector board **1611**. As described in further detail later in this specification, pin connector board **1611** is electrically connected to a controlled voltage source. The coupled pins **1623** pass through holes (not shown) in electronics housing **1610**, holes (not shown) in vacuum manifold housing **1620** and holes **1632** (*see* FIG. 15) in gasket **1630** to contact the electrical contact pads (not shown in FIG. 13) of electrostatic chuck **202**. Such electrical contact pads are depicted, for example, in FIG. 11, as pads **208** located on second surface **206** of electrostatic chuck **202** (*see also*, pads **308A-308C** of FIGS. 12a-12c).

A conductive adhesive, such as conductive epoxy, is applied to a lower region of lower pin assemblies **1624** such that the adhesive adheres the lower pin assemblies to the electrical contact pads. Notch **1626** in lower pin assembly **1624**, as shown in a top view of lower pin assembly **1624** depicted in FIG. 16, allows excess conductive adhesive to be displaced from the region at which the lower pin assembly contacts the electrical contact pad.

The above-described arrangement for providing electrical connection to powder-attracting electrodes **307** advantageously avoids deforming electrostatic chuck **202**, which in most embodiments is relatively susceptible to deformation. It is advantageous to avoid such deformation because, if the electrostatic chuck deforms, then the substrate adhered thereto will likewise deform. Deformation of the substrate is undesirable because it is preferable to deposit powder on a "flat" substrate. Thus, while other arrangements for providing electrical connection to the powder-attracting electrodes, as may occur to those skilled in the art in view of the present teachings, may suitably be used, such arrangements will advantageously avoid deforming the electrostatic chuck.

Gasket **1630**, depicted in FIG. 15, includes slots **1631** that allow reduced pressure to be transmitted to electrostatic chuck **202**. Gasket **1630** further includes holes **1632** that allow coupled pins **1623** to be inserted through the gasket **1630**, as previously described. Gasket

1630 preferably insulates at least about 2,000 - 2,500 volts. In one embodiment, gasket 1630 is coated on both sides with adhesive. A material suitable for use as gasket 1630 is a graphics art paper having a thickness of 0.004 inches (0.1 mm) that is coated on both sides with an aggressive rubber-based adhesive. Such paper is commercially available from Cello-Tak of Island Park, New York.

FIGS. 17 - 22 depict additional detail of an illustrative embodiment of receiver 172, and an arrangement for connecting the receiver to first robotic transport element 170.

FIG. 17 depicts underside 1730 of receiver platform 1720 of illustrative receiver 172 with electrostatic chuck 202 adhered thereto. Electrostatic chuck 202 has alignment features 240, such as pins or holes, by which it is aligned to complementary holes or pins 1629 in receiver platform 1720 (*see* FIG. 18). Also depicted are alignment pins 1650 that are received by complementary holes in support bench 110 for aligning receiver 172 to various processing stations (*e.g.*, deposition station 150). Height-adjustable vacuum cups 1670 are advantageously used to attach the substrate frame (not shown) to the receiver.

FIG. 18 depicts underside 1730 of receiver platform 1720 without electrostatic chuck 202. FIG. 18 shows passageways 1622 for conveying reduced pressure to through holes ECH in electrostatic chuck 202 (through holes ECH not shown in FIGS. 17 and 18; *see* FIGS. 10 and 11) and to passageway outlet 1628. Pin conduits 1623A allow passage of coupled pins 1623 to electrical contact pads on electrostatic chuck 202. Further shown are alignment features 1629, which can be, for example, alignment pins or alignment pin receptacles for mating with alignment features 240 of electrostatic chuck 202.

FIG. 19 shows upper side 1710 of receiver platform 1720. Receiver platform 1720 includes passageway outlet 1628, pin conduits 1623A and moldings that form reinforcing braces 1780. As illustrated in FIG. 20, braces 1780 on upper side 1710 support processor board 1614, addressing board 1615 and high-voltage board 1612 (*i.e.*, bias-generation board). Electrical communication to electronics located off of receiver 172 can be accomplished via port 1616. Tubing connector 1627B connects receiver 172 to an external vacuum source for developing reduced pressure through vacuum manifold housing 1620, *etc.*, for adhering substrate assembly 82 to electrostatic chuck 202.

FIG. 20 also depicts a substrate frame, such as substrate frame 81, engaged to underside 1730 of receiver platform 1720 (electrostatic chuck not shown). Substrate frame 81 includes alignment features 52 that suitably engage complementary alignment features at

alignment station **130**.

FIGS. 21 and 22 depict an arrangement by which receiver **172** is engaged to robotic transport element **170** (depicted in FIG. 8), as well as showing additional features associated with receiver **172**. FIG. 21 provides a "cutaway," along the indicated perspective, of the view indicated in FIG. 22.

In the illustrative embodiment depicted in FIGS. 21 and 22, receiver **172** is mounted to first robotic transport element **170** (not shown) via bearing housing **1120**. Bearing housing **1120** contains spline shaft **1121** and spline shaft bearings **1122**. Bearing housing **1120** allows receiver **172** to be moved along the z-axis. Bearing housing **1120** couples to floating bolt assembly **1640** via spring-loaded coupling **1130**. Floating bolt assembly **1640** (*see* FIG. 22) mounts to receiver cover **1660** via bushings **1641**, which may be visco-elastic isolation bushings **1641**. Such visco-elastic isolation bushings can be made, for example, from Sorbothane® brand isolation damping material commercially available from Sorbothane, Inc. of Kent, OH. The visco-elastic isolation bushings **1641** advantageously allow receiver **172** to move slightly, as required, when receiver locating pins **1650** (*see* also FIG. 17) are inserted into alignment holes located on support bench **110**. In this manner, the locating accuracy of robotic head **170** (±2 mil) can be increased (to about ±0.5 mil) when base substrate **80** is presented for dry deposition at deposition station **150**. Floating bolt assembly **1640** allows receiver **172** to comply with alignment actions acting in a direction along the x, y or z axes.

In the embodiment depicted in FIG. 21, receiver **172** includes pin connector board **1611**, high-voltage board **1612**, high-voltage chip areas **1613** and processor board **1614**. In other embodiments, processing is orchestrated via a processor located elsewhere on robotic platform **101**. High-voltage barrier wall **1661** isolates the high voltage areas of receiver **172**. Illustrative receiver **172** further includes vacuum tubing **1627**, first tubing connector **1627A** for connecting vacuum tubing **1627** to vacuum manifold housing inlet fitting **1621** (*see* FIG. 9), and second tubing connector **1627B** previously described.

Substrate frame **81**, on which substrate **80** is mounted, is depicted as adhered to the underside of the receiver **172** (electrostatic chuck **202** not shown). As discussed further below, the frame advantageously assures that the substrate is aligned with a post-deposition measurement device. Vacuum cup receiving fixtures **51**, which are disposed on substrate frame **81**, receive height adjustable vacuum cups **1670** in vacuum-facilitated engagement. Vacuum hose fittings **1671**, which are connected to a vacuum system, are in fluid

communication with vacuum cups **1670**.

Portions of receiver **172** (*e.g.*, receiver cover **1660** in FIG. 22) are advantageously manufactured from a durable non-conductive material such as, for example, plastic. Examples of suitable plastics include Noryl® brand polymers commercially available from GE Plastics of Pittsfield, MA. Noryl® engineered plastics are modified polyphenylene oxide, or polyphenylene oxide and polyphenylene ether, resins. Modification of these resins involves blending with a second polymer such as polystyrene or a mixture of polystyrene and butadiene. By varying the blend ratio and other additives, a variety of polymer grades are produced. Unmodified, these polymers are characterized by regular closely-spaced ring structures (*i.e.*, phenyl groups) in the main molecular chain. This feature along with strong intermolecular attraction causes extreme stiffness and lack of mobility.

Use of Noryl® brand plastics or equivalent imparts a strength to receiver **172** that aids in providing a firm, flat support for electrostatic chuck **202**. The surface of receiver **172** on which electrostatic chuck **202** is mounted is advantageously machined flat, for example to ± 0.001 inches (0.025 mm). Moreover, the characteristic low weight of the plastic assists in keeping the weight burden low on first robotic transport element **170**.

Electronic Control of the Electrostatic Chuck

As previously described, apparatus **100** advantageously includes central processor **401** and controller **403** for performing calculations, control functions, *etc.* (*see, e.g.*, FIG. 6). Processor **401** receives performance input from multiple sources, including, for example, on-board sensors and historical data from dose measurement station **140**, and uses such information to determine if operating parameters should be adjusted to keep powder deposition within specification. Such input includes, for example, data pertaining to the rate of powder flux into and through the deposition engine (made up of powder feed apparatus **801** and deposition station **150**) and the degree to which powder is being evenly deposited at electrostatic chuck **202**. The "on-receiver" electronics described below, either alone or in conjunction with processor **401** and controller **403**, provide a means for adjusting apparatus **100** during operation.

When processor **401** has primary responsibility for processing functions, processor board **1614** located in receiver **172** can function as a communications board that receives commands from processor **401** and relays such commands to addressing board **1615**. In

some embodiments, processor board **1614** receives data from sensors, such as charge sensor **1690**, that are positioned on or adjacent to electrostatic chuck **202** (*see* FIG. 18, wherein charge sensor **1690** is represented figuratively by dashed lines). Charge sensor **1690** is an on-the-receiver device for monitoring the amount of powder being deposited. Processor board **1614** locally interprets and responds to data from charge sensor **1690** by suitably adjusting the voltage applied to the powder-attracting electrodes **307** (*e.g.*, electrodes **307A - 307C** in FIGS. 12a - 12c, respectively) as appropriate. Charge sensors are described further below and in U.S. Pat. App. 09/095,425.

After receiving signals from processor board **1614**, addressing board **1615** sends bias control signals, which can be, for example, DC or AC signals, for controlling the voltage at powder-attracting electrodes **307**. Depending upon the addressing scheme (*e.g.*, the arrangement, if any, by which individual electrical-contact pads **208** are electrically interconnected via address electrodes **210**), voltage is either regionally (*e.g.*, by columns, rows, *etc.*) or individually applied to powder-attracting electrodes **307**.

Addressing board **1615** preferably has multiple channels of synchronized output (e.g., square wave or DC). The signals sent to the addressing board can be encoded, for example, with a pattern of square wave voltage pulses of varying magnitudes to identify a powder-attracting electrode **307**, or a group of such electrodes, together with the appropriate voltage to be applied thereto.

The bias control signals are sent via high voltage board **1612**, which advantageously has multiple channels of high-voltage converters (transformers or HV DC-to-DC converters) for generating the voltages, such as 200 V or 2,500 V or 3,000 V (of either polarity), that energizes powder-attracting electrodes **307**. Such high voltages are advantageously formed within receiver **172** so that other systems are isolated therefrom.

The Charge Sensor

The charge sensor **1690**, mentioned above, advantageously uses pulsed (AC) electrical potential waveforms for biasing the electrostatic chuck to collect powder on substrate **80**, as is described in U.S. Pat. App. No. 09/095,425. This form of biasing overcomes the problem of collecting powder on a conductive substrate, where the powder-attracting field can decay rapidly after any given application of a bias potential to the

electrostatic chuck.

Using AC bias waveforms for the powder-attracting electrode also solves another long-standing problem during deposition sensing. In particular, during deposition sensing, one or more collection zones **CZ** are closely monitored for powder accumulation, so as to allow regulation of the powder deposition process (*e.g.*, to produce precise dosages). Such monitoring can be performed optically or by measuring accumulated charge using an "on-board" charge sensor at a sensor-associated collection zone. Accumulated charge can be correlated to actual charged powder deposition by empirical data collection. In dry powder deposition, such dose monitoring is often a very difficult task, particularly for dosages below one milligram.

The difficulty lies not with the precision of the measuring devices, but rather with various practical and environmental factors that can deteriorate measurement sensitivity by two or three orders of magnitude. For quasi-static DC-biased transporter chucks, on-board charge sensing is particularly difficult. Data obtained by depositing on a polypropylene film substrate with different potentials indicates that the deposited dose is linearly related to the bias potential if that potential is above a certain threshold potential. Data indicates that threshold potential is about 100-200 volts DC, at least for certain transporter chucks.

FIG. 40 shows one possible equivalent circuit diagram that provides AC-biased charge and deposition sensing for at least one collection zone **CZ**, which zone has a floating pad electrode. The floating pad electrode is an isolated conductor which is designed to be capacitively coupled to a powder-attracting electrode (*e.g.*, powder-attracting electrodes 307A- 307C of FIGS. 12a-12c, respectively) such that the bias to the powder-attracting electrode indirectly creates a powder-attracting field emanating from the floating pad electrode.

An illustrative electrostatic chuck/substrate arrangement corresponding to the equivalent circuit of FIG. 40 includes a planar electrode that is used to provide a powder-attracting field. A bottom face of the planar electrode is affixed to an upper face of a planar first dielectric layer such that such faces are parallel to one another. Suitable dielectric material includes Pyrex 7740 glass available from Corning, Inc., or polyimide resin having a thickness of about 10 to 20 mils. The planar electrode and planar first dielectric layer can be affixed to one another using a variety of suitable methods such as, for example, lamination, powder deposition or thin film deposition. A planar shield electrode is affixed to a bottom

face of the first dielectric layer. The shield electrode comprises an aperture to accommodate a floating pad electrode, coplanar with and surrounded by the shield electrode.

One or more collection zones **CZ** are typically dedicated solely for sensing or, alternatively, are in general use, but closely monitored. By measuring the lowering of the attraction potential V_{BCZ} that occurs as charged powder deposits on the collection zone **CZ**, a measure of the deposited charge can be obtained. Knowing the average charge/mass ratio **q/m** of the deposited powder, the accumulated powder deposition mass can be determined. V_{BCZ} can be measured directly across a charge-collector electrode, but it is usually preferable to measure the potential across a coupling capacitor, such as the floating pad electrode described above.

The coupling capacitor, as embodied by the aforedescribed floating pad electrode, provides reasonably accurate reproduction of the potential at the collection zone **CZ** on the substrate surface. Such accurate reproduction is shown by examining waveforms **3602** for V_{BCZ} and waveform **3604** for $V_{Pad\ F}$ depicted in FIG. 41. RC decay is evident in waveforms **3602** and **3604**. Waveform **3606** represents the pulsed bias voltage V_g. Whether a charge collector or charge coupling capacitor is used, they may both be considered charge sensing electrodes.

In the equivalent circuit of FIG. 40, charge collector/coupling capacitor **CC** is electrically connected to a separate sensing capacitor **SC**. The voltage generated across sensing capacitor **SC** can be a reliable indicator of the potential V_{BCZ}. Such voltage can be measured, for example, with an electrometer **M**, such as a Keithley model no. 614, 6512, 617, 642, 6512, or 6517A electrometer, as shown schematically in the figure. Generally the coupling capacitor **CC** is any electrode that is capacitively coupled to a powder collection zone on the contact surface.

DC biasing can cause a steady drift in the reading of the potential across the sensing capacitor. Such drift is due predominantly to natural leakage across the dielectric material in the sensing capacitor, and to charge leakage in the substrate or powder that has accumulated on the chuck. Drift can also be induced by noise factors such as shot noise, Johnson (1/f) white noise, thermal noise, Galvanic noise, triboelectric noise, piezoelectric noise, amplifier noise, and electromagnetically-induced noise. *See, The Art of Electronics*, by Paul Horowitz, Winfield Hill, 2nd Edition, Cambridge University Press, © 1989.

If the drift is large compared to the actual charge collected at a collection zone **CZ**, the accuracy of the charge sensor as a measurement tool can be unacceptably low. Using AC biased waveforms as disclosed herein advantageously reduces the incidence of drift. Such a reduction is accomplished in a manner similar to that described above for avoiding the "drift" of charge dissipation on the powder collection zone, facilitating precise measurement of charge collected.

In FIG. 40, an AC bias source **B** may be the same source as described above, with the AC bias potential applied or administered via the powder-attracting electrode. This electrically couples to the floating pad electrode or to the collection zone itself, if it is directly connected to the sensing capacitor as shown.

By way of example, if sensing capacitor **SC** is chosen to be 0.1 μF, and the **q/m** of the powder is 10μC/g, then a 100 mV signal change on the charge collector/coupling capacitor **CC** corresponds to 1 mg of powder deposited on the collection zone. If, for example, the linear correlation factor is 3, then 1 mg of powder on the sensor corresponds to 3 mg of powder in the actual deposition dose. A 99 μg actual dose will thus have a detectable potential change of 3.3 mV. With a 5% error tolerance, the corresponding background unpredictable noise contribution cannot exceed 160 μV. This is achievable with careful shielding and grounding design. Preferably the charge collector is integrated with the chuck design to assure a consistent correlation.

In effect, the same benefits obtained using the AC bias waveform for V_g to avoid charge dissipation in the substrate can be used to reduce drift in the charge sensing circuit.

FIG. 42 depicts another possible equivalent circuit for providing AC-biased charge and deposition sensing. The illustrative circuit of FIG. 42 reduces noise by separating the AC bias source **B** from electrometer **M**, sensing capacitor **SC** or charge collector/coupling capacitor **CC**. All of those components have a sensitivity to noise that is critical.

As depicted in FIG. 42, AC bias source **B** is connected to the primary of a transformer **T**. In this manner, only the periodic magnetic field generated by **Vg**, (not **Vg** itself) is introduced into the "sensitive" components on the right side of the figure. The secondary winding of transformer **T** is connected across a stabilizing bleed resistor **R**, with one pole (*i.e.*, biasing pole **BP**) connected to charge collector/coupling capacitor **CC**, and the other pole (*i.e.*, the sensing capacitor pole **CP**) connected to sensing capacitor **SC**. To further reduce noise, sensing capacitor **SC** is connected to ground. Electrometer **M** can then

measure the voltage change on sensing capacitor SC with respect to ground, as shown. The two grounding points can be combined to further reduce electromagnetic noise. Transformer T can be a step-up transformer so that complex AC bias waveforms supplied here and to the powder-attracting electrode can be generated inexpensively. A step-up ratio of 50, for example, may suitably be used. Such an arrangement substantially reduces drift and makes accumulated charge sensing more accurate, where previously a coupling current of 100 pico-Amperes or less made drift and noise a problem.

In some embodiments, transformer T is an isolation transformer, where the primary and secondary windings are separated by a Faraday cage. This can prevent coupling between the primary and secondary windings, where the primary winding acts as one capacitor plate, and the secondary as the other capacitor plate.

As a result of the improved signal to drift ratio obtained in accordance with the present teachings, the amount of charge sensed can decrease substantially. Measurements can be made using a 1000 picoF capacitor as the sensing capacitor instead of the 0.1 μF value used previously. Also, AC bias source **B** used in the circuits depicted in FIGS. 40 and 42 can be separate from the AC waveform bias **Vg** on the chuck, by delivering a separate AC bias directly to charge collector/coupling capacitor **CC** via a dedicated wire, electrode, bus, etc. Such a separate AC bias can be frequency matched or detuned with respect to **Vg** to insure consistent correlation of the behavior of the charge collector/coupling capacitor **CC** to actual depositions.

The aforedescribed arrangements advantageously allow **Vg** biasing with voltage peaks much higher than previously possible. Using 8000 molecular weight polyethylene glycol as a substrate, bias peaks of 2 kV have been used. It should be understood a wide variety of transporter chucks can suitably be used, including those that operate with bias electrodes directly exposed to the powder contact surface (*i.e.*, the substrate), such as is illustrated in FIGS. 12a and 12b.

The Alignment Station

As previously described, electrostatic chuck **202** (engaged to receiver **172** and first robotic transport element **170**), engages frame **81** containing substrate **80** at input/output station **120A**, and then delivers it to alignment station **130** (*see, e.g.*, FIGS. 7, 8, 9 and 21).

At alignment station **130**, frame **81** is released from electrostatic chuck **202**/receiver **172** so that alignment features **52** of frame **81** (*see* FIG. 20) matingly engage complementary alignment mechanisms (not shown) at the alignment station. Such alignment features may be, for example, pins on frame **81** that are received by holes at alignment station **130**. Frame **81** is then re-engaged by the electrostatic chuck and receiver, and, as a result, substrate assembly **82** is now aligned to within the accuracy of robotic transport element **170** (e.g., ± 0.002 inches (0.05 mm)).

In some embodiments, a visco-elastic pad (not shown), such as a foam rubber pad, is included at alignment station **130**. When substrate assembly **82** is re-engaged, substrate **80** is pressed against the pad to remove any air pockets that are formed between substrate **80** and electrostatic chuck **202**. With substrate **80** pressed against the pad, the substrate-adhering vacuum of the receiver **172** is activated, and powder-attracting electrodes **307** can also be activated to aid in adhering the substrate to electrostatic chuck **202**.

Alignment station **130** may improve substrate alignment to the electrostatic chuck, especially when misalignment-causing circumstances are present. One such circumstance arises when a substrate frame (*e.g.*, substrate frame **81** or **91**) is stacked on other frames at an input/output substation. It will be appreciated that as frames are successively stacked, the frames may deviate from a properly aligned position. When a robotic transport element (*e.g.*, elements **170** or **180**) engages the frame with a clamping feature, such as vacuum cups **1670** (*see*, FIG. 22), misalignment may occur. Using alignment station **130**, alignment accuracy is improved to within the placement accuracy of the robotic transport element (at alignment station **130**) so that substrate **80**, for example, can be positioned with the requisite accuracy during the deposition operation. Alignment station **130** advantageously provides a secondary benefit whereby the visco-elastic pad facilitates intimate contact between electrostatic chuck **202** and substrate **80**.

Second robotic transport element **180** engages frame **91** containing a cover layer **90** and uses alignment station **130**, in the manner described above, to confirm localization of frame **91**. The second robotic transport element **180** moves cover assembly **92** to lamination support block **1901** (*see* FIG. 23, frame **91** not shown) and deposits it thereon.

The alignment features described above are suitable for processing substrates in batch or piece-wise fashion, as in the illustrated embodiments. Alignment issues are advantageously addressed in a different manner in the context of continuous processing

operations. For example, if, in a continuous process, the substrate is deployed on a tape, then frames can be periodically locked to the tape as it is processed through portions of the present apparatus where alignment issues are particularly important. To provide adjustment capability for such a process, a small amount of loosely fitting tape can be employed between the locked frames, thereby allowing the spacing between the frames to be adjusted based on alignment considerations.

Framing and alignment considerations are described further later in this specification with reference to deposition station **150** and dose measurement station **140**, where alignment is particularly important.

Deposition Engine

In one embodiment, after substrate assembly **82** is aligned at alignment station **130**, first robotic transport element **170** moves the substrate assembly to deposition station **150**. In another embodiment, substrate assembly **82** is first moved to dose measurement station **140** so that baseline optical data can be recorded before the powder-deposition operation, and then robotic transport element **170** moves substrate assembly **82** to deposition station **150**.

Robotic transport element **170** is rotated 90° to align frame **81** of substrate assembly **82** with deposition opening **158** (*see* FIG. 7) at deposition station **150**. Locating pins **1650** (FIGS. 17 & 22) are used to establish the alignment of receiver **172** / electrostatic chuck **202** / substrate assembly **82** with deposition opening **158**.

An illustrative deposition engine **800** is illustrated in FIG. 24. Deposition engine **800** includes deposition station **150** and illustrative powder feed apparatus **801**. A deposition engine presents the possibility for a variety of processing problems. Such problems include, for example, powder compaction, non-uniform powder flux, powder loading, operating stability and powder size limitations, among others. In some applications, such problems can be addressed by modifying the powder. The present invention, however, is intended to be useful for applications, such as pharmaceuticals, in which there is often little or no ability to modify powder without raising regulatory issues. As such, the deposition engine itself should be designed to avoid such difficulties. Various components of illustrative deposition engine **800** can improve the deposition operation, resulting in: decreased powder compaction, more uniform powder flux, ease of powder loading, improved operating stability, the ability to use a wide variety of powder particle sizes, and improved powder flow

without the powder surface modifications that are often performed in other applications.

Illustrative powder feed apparatus **801** includes auger rotation motor **804**, hopper **806**, vibrator **808**, auger **810**, clean gas source **814** feeding modified venturi feeder valve **812**, powder charging feed tube **816**, powder evacuation tubes **818**, powder trap **820**, and High Efficiency Particulate Air (HEPA) filter **822**, interrelated as shown. Illustrative powder feed apparatus **801** is disposed substantially within enclosure **802**, which is depicted in phantom for clarity of illustration.

In operation, auger **810** is rotated, via auger rotation motor **804**, to feed powder into venturi feeder valve **812**. A rotational rate within the range of about 10 to about 80 rotations per minute is satisfactory for such purpose. Modified venturi feeder valve **812** having a venturi well that delivers powder in a substantially straight path from the auger feed (*i.e.*, hopper **806**) to powder charging feed tube **816** was used. Such a modified device avoids powder compaction that may be experienced when powder fall to the bottom of the venturi well in standard arrangements. The venturi well should be accessible, for example, by an unscrewing action, so that it can be periodically vacuumed.

Vibrator **808** is advantageously used to keep the powder free-flowing, with vibration intensity set at a level that does not cause substantial aggregation of the powder. The vibrator is illustrated as acting on the hopper **806**, but can likewise be applied to a shaft driving a mechanical powder-moving appliance such as auger **810**.

When a flow of gas, such as, for example, nitrogen, from clean gas source **814** is admitted to modified venturi feeder valve **812**, powder is pulled from auger **810**. Moreover, such gas acts to push the powder through powder charging feed tube **816**. A modified venturi suitable for use in the powder feed apparatus **801** is commercially available from Vaccon Company, Inc. through Air Oil Systems, Mainland, PA, or Berendsen Fluid Power, Rahway, NJ.

In place of a venturi, a gas source can be provided to propel powder through powder charging feed tube **816**. In one embodiment, gas source **814** directs gas pressure towards the outlet of a mechanical device that feeds powder. The gas jet can be directed and adjusted to act to deagglomerate powder at that outlet.

For electrostatic deposition, the powder must be charged. In one embodiment, powder charging feed tube **816** is made of a material that imparts, by triboelectric charging, the appropriate charge to the powder as it transits the tube making periodic collisions with

the sides thereof. As is known in the art, TEFLON®, a perfluorinated polymer, can be used to impart a positive charge to the powder (where appropriate for the powder material) and Nylon (amide-based polymer) can be used to impart a negative charge. In so charging the powder, the tube builds up charge which can, if not accommodated, discharge by arcing. Accordingly, a conductive wrap or coating is applied to the exterior of powder charging feed tube **816** and grounded. Tube **816** can be wrapped, for example, with aluminum or copper foil, or coated with a colloidal graphite product such as Aquadag®, available from Acheson Colloids Co. of Port Huron, MI. Alternatively, powder charging feed tube **816** can be coated with a composition comprising graphite or another conductive particle such as copper or aluminum, an adhesive polymer, and a carrier solvent, mixed in amounts that suitably preserves the "tackiness" of the adhesive polymer. An example of such a composition is 246 g trichloroethylene, 30 g polyisobutylene and 22.5 g of graphite powder.

The charge relieved by the grounding procedures outlined above can be monitored to provide a measure of powder flux through powder charging feed tube **816**. This data is advantageously sent to processor **401** for analysis. As a result of such analysis, deposition operating parameters can be modified, as appropriate, to maintain an on-specification operation. An illustrative arrangement suitable for providing such monitoring is described below.

In one embodiment, a capacitor is placed in series with powder charging feed tube **816**. The capacitor lowers the potential generated by the charges collected in the tube **816**. A 1 μF capacitor will build up 1 V for a 1 μC charge. The other pole of the capacitor is connected to ground. The capacitor acts to bring the potential of the powder charging feed tube **816** closer to ground. An electrometer connected to the capacitor provides an accurate measure of collected charge. With powder charged to 50 μC/g, 1 μC corresponds to 20 mg of powder. Powder charging feed tube **816** can be biased. With an applied bias of 500V, noise of 10 pA can be anticipated, creating an uncertainty of 3 nC over 3 minute intervals. Even with such biasing, such a system provides errors as low as 0.3% on measurement of 20 mg of powder. By controlling the conductivity of the grounding wrap or coating, a potential drop along powder charging feed tube **816** can be established, creating an electric field that favors drawing charged powder through the tube while giving uncharged powder greater opportunity to pick up charge.

Another way to impart charge to the powder is by "induction" charging. One way to

implement induction charging is to incorporate an induction-charging region in powder charging feed tube **816**. More particularly, at least a portion of powder charging feed tube **816** comprises a material such as a stainless steel, which is biased by one pole from a power supply, with the opposite pole grounded. With an appropriate bias, an electric field is created in the induction-charging region such that powder passing through it picks up a charge. The length of the induction-charging region can be adjusted as required to impart the desired amount of charge to the powder. In one embodiment, induction charging is used in conjunction with the tribocharging features described above.

Powder charging feed tube **816** feeds charged powder into deposition station **150** via nozzle **152**. Deposition station **150** is enclosed by enclosure **154**, comprising, for example, acrylic panels. Nozzle **152** advantageously includes rotating baffle **153** that increases the uniformity of the powder cloud developed in deposition station **150**. Nozzle motor **151** drives rotating baffle **153**.

An illustrative nozzle **152** with rotating baffle **153** is shown in more detail in FIGS. 25 (plan view) and 26 (side view). Rotating baffle **153** comprises baffle disk **1552** that is supported by three spaced, radially-extending baffle supports **1551**. Baffle disk **1552** includes baffle outlets **1553** through which the powder passes. In the embodiment depicted in FIG. 26, which is drawn approximately to scale, the height BH of rotating baffle **153** is about 0.72 inches (18 mm).

Powder is fed through the nozzle **152** with, for example, a gas that is at a pressure of about 20 psi and fed at a rate of about 2.5 liters per minute. The gas is preferably substantially free of water, oil and other impurities, and is preferably a chemically inert gas such as nitrogen or helium. Baffle **153** is advantageously disposed above the outlet of powder charging feed tube **816** by an amount in the range of about one-quarter to one-half inch. Moreover, baffle **153** advantageously has a larger diameter or cross-section than the outlet of powder charging feed tube **816**. For example, baffle **153** may have a one-half inch diameter cross section when a one-quarter inch diameter powder charging feed tube **816** is used. Baffle **153** should be rotated at a rate within the range of about 5 to about 25 rotations per minute to obtain the desired increase in uniformity of the powder cloud.

Referring again to FIG. 24, substrate assembly **82** and electrostatic chuck **202** (both not shown) abut gasket **159** that frames deposition opening **158**. Powder moving towards collection zones **CZ** of electrostatic chuck **202** pass through control grid **157**. Control grid

157 is advantageously disposed a distance d_{grid}, for example about one-half to about 1.0 inch, below the collection zones, and is biased at about 500V per one-half inch of distance d_{grid} at the polarity intended for the powder. Control grid **157** thus "collimates" the powder cloud attracting powder having an opposite charge (to the charge on the control grid).

Control grid **157** can be, for example, a series of parallel electrical wires, such as can be formed from "switchbacks" of one wire, or, alternatively, a grid of wires. Spacing between parallel sections of wire is advantageously within the range of about 5 to about 15 mm.

The rate of powder cloud flux can be monitored by measuring light attenuation between light emitter **155** (*e.g.*, a laser emitter) and light detector **156**. This value can be transmitted to processor **401**.

Powder that is not utilized at deposition station **150** are drawn back by a pressure differential through powder evacuation tubes **818** to powder trap **820**. FIG. 27 depicts internal detail of an illustrative embodiment of powder trap **820**. Powder enters powder trap **820** via trap inlet **2104**. Powder trap **820** includes a series of conductive first baffles **2101** interleaved with conductive second baffles **2102**. To provide the requisite conductivity, the first and second baffles can be formed of materials such as copper, stainless steel or aluminum baffles, for example. The first and second baffles **2101** and **2102** are affixed to respective first trap electrical conduit **2107** and second trap electrical conduit **2109**. First and second trap electrical conduits **2107** and **2109** are affixed to trap body **2103**. Trap body **2103** is formed, for example, of acrylic polymer (*e.g.*, plexiglass).

First baffles are biased at, for example, +2000V, via first trap electrical conduit **2107**, which is in electrical communication with first electrical inlet **2106**. The second baffles are biased, for example, at -2,000V, via second trap electrical conduit **2109**, which is in electrical communication with second electrical inlet **2108**. Powder returning from deposition station **150** are collected on oppositely charge baffles. When powder is uncharged, a first collision with one baffle can impart a charge, allowing the powder to be attracted to an oppositely-charged baffle that it encounters downstream. Gas exiting powder trap **820** through powder trap outlet **2105** is delivered to HEPA filter **822** (not shown in FIG. 27, *see* FIG. 24). HEPA filter **822** is typically 99.97 percent efficient in capturing 0.3 micron powder particles, thereby assuring that no more than a relatively insignificant amount of powder, which powder can be detrimental as bioactive agents (without dosing control), is released into the

environment.

At some point, the deposition process must be shutdown. Such shutdown may be dictated, for example, by schedule (*e.g.*, where the amount of powder that is deposited is controlled by the period of operation) or in response to the analysis of feedback data from a charge sensor. Shutdown involves reducing the voltage (or the amplitude in the case of a pulsed voltage profile) directed to powder-attracting electrodes **370**, and shutting down powder feed apparatus **801**. The amount of voltage reduction required for shutdown will vary as a function of the substrate and powder specifics, as well as the amount of powder applied to the substrate. Generally, such voltage reduction is selected to maintain substrate adherence to electrostatic chuck **202**, and powder adherence to substrate **80** without causing substantial further powder accumulation. By way of example, stepping down a 2000V deposition voltage (or voltage amplitude where pulsed voltage is utilized) to 400V should be sufficient to retain powder but not attract additional powder.

It should be appreciated that other arrangements or configurations for deposition station **150**, as well as for many of the other elements of powder deposition apparatus **100** described herein, may suitably be used in conjunction with the present invention. For example, a first alternate embodiment of a receiver, an electrostatic chuck, and a nozzle (as included at deposition station **150**) is depicted via side view in FIG. 28 and via top view in FIG. 29. In the depicted first alternate embodiment, receiver **572** is configured as a rotatable drum. Similarly configured electrostatic chuck **502** is engaged to receiver **572**. As in previous embodiments, substrate **580** abuts electrostatic chuck **502**. Axle **501** imparts rotation to receiver **572** and advantageously conveys (e.g., through internal conduits, *etc.*) vacuum and electrical potential to collection zones (not shown) on electrostatic chuck **502**. In some embodiments, axle **501** is also operable to move receiver **572** "up and down" relative to four radially-arranged nozzles **552** (only two of which are depicted in FIG. 28). Grids **557** limit access by improperly charged powder to the collection zones. Variations in the deposition pattern can be minimized by rotating receiver **572**.

It should be understood that various elements of the powder feed apparatus depicted in FIG. 24 may be suitably interchanged or replaced by elements performing equivalent functions. For example, the hopper and auger arrangement depicted in FIG. 24 can be replaced with a rotating drum that temporary stores powder and delivers it to a movable belt. The movable belt then transports the powder to a means for removing the powder from the

belt. An example of such a means is a thin, high velocity, jet of gas that blows the powder into powder charging feed tube **816** (FIG. 24) or a conduit in communication therewith.

Alternatively, the powder feed apparatus may be configured in a substantially different manner from the apparatus **801** depicted in FIG. 24. Two such alternative configurations that are suitable for use in conjunction with the present invention are depicted in FIGS. 30 and 31.

FIG. 30 depicts powder feed apparatus **901**, in which hopper **907** directs powder to gear wheel **905** that is driven by motor **903**. Gas flow **909** directs powder to deposition station **150**. Electrostatic chuck **202**, electrically connected to high voltage source HV, is depicted in position at deposition station **150** receiving powder at its collection zones.

FIG. 31 depicts powder feed apparatus **1001** comprising fluidized bed **1003**. Gas flow **1009** directs powder to deposition station **150** through four powder charging feed tubes **1016**. While four such tubes are depicted in FIG. 31, more tubes, or as few as one tube may suitably be used.

In some embodiments, particularly wherein doses such as about 2 μg to about 100 μg are applied to an area of 3 to 4 mm diameter, a jet mill can be favorably employed to deliver powder. Charge can be introduced to the powder by induction charging by applying a potential to the jet mill itself, such as applying a 1,800V potential to the jet mill. A jet mill suitable for such service is available from Plastomer Products Division of Coltec Industrial Products Inc. (Newton, PA) under the mark TROST® Air Impact Pulverizer. That jet mill utilizes directly opposing streams of compressed gas, and is usefully operated at a flow rate of about 2.0 to 2.2 liters per minute.

Dose Measurement Station

After completing powder deposition, first robotic transport element **170** moves substrate assembly **82** containing powder-bearing substrate **80** to dose measurement station **140** (*see, e.g.*, FIGS. 7 and 8). Robotic transport element **170** is rotated 90° to align frame **81** with measurement opening **146** (*see* FIG. 8). Receiver locating pins **1650** (*see* FIG. 22) are used to align receiver **172** with measurement opening **146** to an accuracy of about ±0.0005 inches (0.013 mm). Such alignment accuracy assures that the dose measurements are taken at the proper locations on substrate **80** (*i.e.*, the locations at which the powder is deposited).

In embodiments that do not use frames, such as frames **81** or **91**, or another

mechanism for assuring consistency of alignment at the deposition station and the dose-measurement station, the dose-measurement system advantageously includes a mechanism for identifying the positions of the powder depositions. In one embodiment, such a mechanism includes a video camera that collects data and further includes suitable electronics for analyzing the video data to determine the boundaries of the depositions. The video camera can be, for example, a CCD.

Dose measurement station **140** includes an apparatus for measuring the thickness (*i.e.*, the amount) of powder deposited on substrate **80**. Either of two (or both) optical measurement methods may be used: diffuse reflection and optical profilometry. Diffuse reflection has been used for many years to characterize powder using light sources that emit in a range that is absorbed by the powder. In conjunction with that technology, a theory was developed for diffuse reflection using non-absorbing radiation. The theory derives a term for the thickness of a powder layer. In spite of such utility, to the applicants' knowledge, no products based thereon have been commercially developed. Applicants have discovered that measurements obtained based on diffuse reflection using non-absorbing radiation provide a strong correlation with the deposited amount of powder in a unit form, at least up to a certain amount. The limiting amount varies with the character of the powder and is believed to correspond to an amount of powder that prevents light penetration into lower layers.

The diffuse reflection method is based on reflecting or scattering a probe light beam, such as a laser beam, off of the powder surface in directions that are not parallel to the specular reflection direction. Such scattered light is generally uniformly distributed. Dose depositions that exhibit this property or behavior are said to be "Lambert Radiators." This behavior ("Lambertian scattering") is an important property for dose weight measurements. The relation between Lambertian scattering and the optical properties of powder are defined by a scattering model developed by Kubelka and Munk.

As described above, non-absorbing radiation is used to create diffuse reflection. Typical radiation is the visible red lines provided by common gas and diode lasers such as 632.8, 635 and 670 nm. When non-absorbing radiation is used and when the dose deposition has a finite thickness, d, the Kubelka-Munk model gives the following relation:

[1] $$Sd = R/(1-R)$$

where: S is a scattering parameter defined by the properties of the particles of the dose deposition;

d is the dose deposition thickness; and

R is the measured diffuse reflection for dose material on substrates with minimal specular diffuse reflectance wherein $R_{substrate} = 0$ is assumed.

Expression [1] can be rewritten as:

[2] $$d = (1/S)\,[R/(1-R)]$$

where: S is assumed to be a constant for a given particle size distribution.

Thus, the thickness of the dose deposition is directly related to the measured diffuse reflectance. If the dose deposition is a Lambertian radiator, as previously defined, the measurement of R is available.

FIG. 32 depicts, figuratively, the diffuse reflection method for characterizing dry powder. Light from light source **3102**, which can be, for example, a low-energy laser, is preferably focused through beam splitter **3104**. Light source **3102** can direct a beam toward substrate **80** that is wider than the individual "mounds" of deposited powder since the rest of substrate **80** will not have powder that gives rise to Lambertian scattering. Reference beam detector **3106** assists in determining the quality and intensity of the focused beam.

When light impinges on powder **3114** that is deposited on substrate **80**, the powder scatter light **SLHT** in all directions. Scattered light **SLHT** is captured by detector **3108**. Preferably, an array of two or more detectors **3108** are used. Amplifiers (not shown) are advantageously used in conjunction with the detectors. The output from the detector(s) **3108** is then connected to a commercial A/D converter (not shown). The resulting digital signal is scanned, such as by using a computer-controlled scanning mechanism **3110**. Scanning mechanism **3110** communicates with processor **401** (not shown in FIG. 32). Processor **401** generates a powder thickness profile and, thus, the dose weight measurements of the depositions.

In one embodiment, the powder can be deposited on a substrate that has a specular surface so that the contribution of the surface of substrate **80** to the diffuse reflected

component is kept acceptably low. Moreover, substrate **80** is advantageously absorptive so that the measurement will not be sensitive to diffuse reflections from its back surface or from the surface of receiver **172**.

Diffuse reflection in a non-absorbing region provides good accuracy in measuring dose deposition amounts ranging from 50-400μg, or even as high as 750 μg to 1 mg, for a 3 or 7 mm deposition dot, depending on the characteristics of the powder. The diffuse reflection method can detect substantially less than a monolayer of powder. If the deposit is more than a monolayer, the probe light beam must partially penetrate the upper layers so that it can be affected by the reflection off of the lower layers to provide an accurate measurement. There tends, however, to be a practical limit (dependent upon the powder) to deposition thickness for it to exhibit Lambertian characteristics. Diffuse reflection is also a measure of the physical uniformity of the dose deposits at the above-listed ranges.

Optical profilometry is useful for obtaining dose measurements that are above the ranges that can be accurately measured by the diffuse reflection method. FIG. 33 depicts, figuratively, an embodiment of the optical profilometry method. When light, such as laser light, from light source **3202** is delivered to deposited powder **3214**, light is deflected at an angle that is indicative of the height of the deposition layer. That height can be readily calculated by triangulation. To improve the coherence of deflected light, such deflected light is received by profilometer lens **3212** before being captured by one or more position sensitive detectors **3208**. The output data from detector(s) **3208** is scanned using a scanning mechanism **3210** to generate a profile of the powder surface.

The profilometer can be, for example, a confocal profilometer. In a confocal profilometer, light is directed to the substrate through a lens system, and returned light passes at least in part through the same lens system, though typically the returned light is reflected to a detection site. A confocal profilometer suitable for use in conjunction with the present invention is available from Keyence (Keyence Corp., Japan, or Keyence Corporation of America, Woodcliff Lake, NJ) as Model LT8105. That model focuses source light through a pinhole, and a similar focusing through a pinhole of the return light helps establish focus. Applying back-and-forth dithering movement to one of the lenses aids in establishing oscillations in the focus that help identify the optimal focus point.

In one embodiment, a slit is used in place of a pin hole, and a spatially resolvable light detector, such as a charge-coupled device (CCD), is used to simultaneously retrieve data

for multiple points along a linear area of substrate **80**. There exists a possibility that poweder-attracting electrodes **370** or some feature of receiver **172** will create strong reflections that can overwhelm efforts to establish the baseline surface of substrate **80**. Since substrate **80** is preferably uniform, such reflections can be normalized. Once material is deposited on substrate **80**, or where the substrate is sufficiently opaque, clean reflections are obtainable.

Substrate **80** is advantageously scanned before the deposition operation to increase the accuracy of the post-deposition scans. The beam is scanned across the surface and the height of the surface from a reference location is established by triangulation. The difference in height from the reference before and after deposition is attributable to the dose weight.

For the illustrated embodiments, the difference in height is calculated for each column of collection zones **CZ**, and for each collection zone **CZ**. Such values are stored in memory **405**, and the differences are displayed as a measure of the dosage amount for each dosage unit. When any of the individual unit dosage amounts are beyond the predetermined amount by the preferred five percent value, those units can be later identified and selectively discarded providing 100 percent inspection with non-destructive testing of the actual amounts of each unit dosage.

Since dry powder is typically a good diffuse reflector, it is also possible to use an optical triangulation system that is optimized for diffuse reflection. To determine the pre-dose surface profile, and to establish the height of the substrate under examination during the post-dose measurement, it is preferred that the surface of substrate **80** is a diffuse reflector. Moreover, substrate **80** is advantageously absorptive so that reflections off of the back surface of substrate **80** or off of receiver **172** are avoided.

For clarity of illustration, the measurements systems of FIGS. 32 and 33 were depicted with only a single light source **3102/3202**. More than one light source can, however, be used in such systems.

In some embodiments, the deposition sites are excited in succession and the powder profile is characterized after each light source excitation through scanning mechanism **3110** or **3210** by moving the scanner, for example, from a first site to a second site and so on until all of the deposition sites are characterized. In other embodiments, more than one deposition site is excited at a time and data is obtained by scanning the sites simultaneously. In such other embodiments, it is desirable to optimize conditions for reducing the interference from

nearby sites that are being simultaneously characterized. This can be accomplished by optimizing the spacing between the deposition sites or by alternating the excitations of different sites.

It is desirable that light source **3102/3202** be movable in different directions. An industrial process grade (x,y) stage **142** (*see* FIG. 8) provides movement in the x and y directions. Light source **3102/3202** can be a solid state laser suitable for industrial applications such as, for example, model LAS-200-635-5 available from LaserMax Inc. of Rochester, NY. The laser is advantageously mounted on detection platform **144** (*see* FIG. 8). Detectors **3108/3208** can be any suitable detector, preferably silicon, such as those sold by UDT Sensors, Inc. of Hawthorne, CA. Alternatively, large-area solar cells can also be used.

It is advantageous to incorporate both types of the dose measurement systems (*i.e.*, diffuse reflectance and optical profilometry) into dose measurement station **140**. By doing so, accurate dose measurements are not limited to one of either low dose or high dose depositions due to the selection of one or the other of the dose measurement systems. FIG. 34 depicts an arrangement that is operable to provide the two modes of dose measurement using a single light source **3302** and a striated substrate **3380**.

Striated substrate **3380**, shown attached to electrostatic chuck **202**/receiver **172**, has surface striations **3381** running in one direction. Such a striated substrate is particularly useful for providing both profile and diffuse reflection measurements. The arrangement of FIG. 34 includes, in addition to light source **3302** and striated substrate **3380**, detectors **3308a** for diffuse reflection measurement mode and position sensitive detectors **3308b**for profilometry measurement mode, and profilometer lens **3313**.

The diffuse reflection measurements are made in a plane that contains the striations, such as plane ***P***, as depicted in FIG. 35. Profilometry measurements are made by positioning the triangulation system with incident and reflected beams in a plane, such as plane ***O***, that is orthogonal to the striation direction, as depicted in FIG. 36. Striations **3381** thus act like a diffuse surface for the profilometry measurement.

Ideally, striations **3381** do not scatter light in a parallel direction, so that any scattered light is attributable to powder on the surface. For both measurements, the substrate is advantageously dyed so that reflections from the substrate's back surface or from receiver **172** do not interfere with profilometry or diffuse reflection measurements.

FIG. 37 depicts an arrangement for dose measurement using two measurement modes, like the arrangement of FIG. 34. In the arrangement of FIG. 37, however, each measurement mode utilizes its own light source. Illustrative detection array **3400** is disposed on support **3402**, which support is disposed on detection platform **144** (not shown in FIG. 37, *see* FIG. 8). The detection array has a diffuse reflectance system comprising diffuse reflectance light source **3404A** and detection zones **3408A - 3408F**. A profilometry system comprises profilometry lens **3413** that is part of a confocal system so that returned light passes through the same lens. Diffuse reflectance light source **3404A** is, for example, offset from a center point of the arrangement where lens **3413** is found. As a result, specular reflections will be centered in an area such as area **3420** away from detector zones **3408A - 3408F**. Such detector zones include detectors that are preferably angled and arranged to only accept light from an appropriate direction.

It should be understood that the powder deposited at a collection zone **CZ** are measured both in area and thickness to provide a volume measure manifesting the amount of powder with a deposit at each collection zone. The above diffuse and profilometer measurements, while described in terms of thickness, are also measured in conjunction with areas that are determined by the scanning beams.

In particular, adjacent measurement beams are closely spaced, for example 1 mm apart, so that the transverse region occupied by a collection zone **CZ** is also measured and considered in the calculations of the amount of powder present at each deposited location. The beams are advantageously about 6 microns in diameter. For a deposition zone of about 4-7 mm, each powder "dot" will be scanned with four to seven scans, respectively. Such scans are then used to calculate the amount of dosage at each collection zone **CZ**. The system stores the calculations for each zone in memory for future selective screening of out-of-specification pharmaceutical or diagnostic unit dosage forms.

EXAMPLE

Polyethylene glycol (PEG) powder in an about 3 mm diameter dot has been deposited onto a Mylar substrate. Diffuse reflectance data was obtained using a laser-based Keyence instrument (Keyence Corporation of America) operating at 670 nm in the "intensity" mode. Data was obtained using different, usually larger, fractions of the diffusely scattered light. The analytical properties of the measurement did not appear to be very

sensitive to the fraction of collected light (*i.e.*, the measurement is, in this context, unusually robust and ideal for use as an industrial measurement process).

The data set forth in Table 1 below was obtained using the diffuse reflection method, and is the basis for the plot **3500** depicted in FIG. 38, for the four points of this data set. The first three data points were highly correlated and the least squares fit gave an R value, which is a measure of correlation, of 0.999 (for perfect correlation, R = 1). The fourth data point showed variation and the least squares fit for the data set as a whole gave an R value of 0.98. Both R values were well within accepted norms for analytical procedures to determine dry powder dose weights.

Table 1, Experimental diffuse reflectance and dose weight data

PEG Dose Weight, Micrograms, by Assay	Calculated R/(1-R)
108.6	0.35
86.6	0.312
50.6	0.254
36.6	0.201

Subsequent measurements showed that a high degree of correlation existed for the diffuse reflection measurements and dose weight for various types of dose samples. Based on such data, the degree of correlation is thought to be closely related to the structure of the dose (*i.e.*, in particular whether the structure exhibits Lambertian characteristics).

Application of a Covering Material

After dose measurement, first robotic transport element **170** moves receiver **172** and subtrate assembly **82** to lamination station **160**. As previously mentioned, a holding signal is applied to electrostatic chuck **202** at collection zones **CZ** to hold the deposited powder to substrate **80** and the substrate to the electrostatic chuck.

At lamination station **160**, substrate assembly **82** (*i.e.*, frame **81** and substrate **80**) is deposited on top of cover assembly **92** (*i.e.*, frame **91** and cover layer **90**), which assembly **92** is engaged to lamination support block **1901** as depicted in FIG. 39 (frames **81** and **91** not

shown; *see also* FIG. 23). Lamination support block **1901** has dimples **1902** into which the indentations of cover layer **90** fit, and further provides support to allow the cover layer and substrate to be pressed together. Alignment mechanisms on frames **81** and **91** and at lamination station **160** assure that the locations with deposited powder on substrate **80** are matched with the indentations, bubbles, *etc.* in cover layer **90**, as illustrated in FIGS. 23 and 39. After the cover layer and substrate are engaged, the holding signal is withdrawn.

After the first robotic transport element **170** moves away, second robotic transport element **180** moves into place above lamination support block **1901**. Second robotic transport element **180** has vacuum cups **1870** (*see* FIG. 8), bonding head **182**, and a pad **1880** that compresses substrate **80** against cover layer **90** before and during the bonding operation. Once in position, second robotic transport element **180** manipulates bonding head **182** to seal all the depositions between the cover layer and substrate thereby forming the unit forms, whether comprising dosage or diagnostic active ingredients. As will be appreciated by those skilled in the art, "bonding" or lamination can suitably be performed using a variety of methods, including, for example, ultrasonics, thermal techniques, or via adhesives. A suitable ultrasonic bonding head is the 900 M-Series™ ultrasonic welder available from Branson Ultrasonics Corporation in Danbury, CT.

When welding is completed, second robotic transport element **180** moves to its idle position and the final package of dosage forms is removed for final processing as appropriate.

The illustrated bonding method is useful when one desires to keep the deposited powder free of admixture with other components such as film polymers, though it will be recognized that this can be achieved in other ways. The illustrated lamination process provides bonds that "ring" the area on which material is deposited, but it will be recognized that more uniform lamination processes are also applicable.

In one embodiment of the invention, placebos are produced by laminating a substrate sans deposit, or on which an inactive substance was dry deposited.

Miscellaneous Considerations

Many ancillary features that are useful in conjunction with the present deposition apparatus are described herein with particularity. For instance, very favorable results are

obtained using one method of aligning the substrate with the deposition station **150** and with the dose measurement station **140**. The illustrated embodiments utilize frames to facilitate such alignment. Those skilled in the art will recognize that many of the features described herein are useful without others that are described, such as a deposition apparatus that does not use frames.

In some embodiments, the electrostatic chuck will be cycled out of the process and reused sooner than in the illustrated embodiments. For example, in embodiments where the substrate is a film that is advanced on rollers, the electrostatic chuck used in deposition can be brought in contact with the film when the film advances to the deposition station, and removed immediately thereafter. If necessary, another chuck can be used to assure that the film is smooth and flat (in most embodiments) when presented to a dose-measurement station. Such an embodiment with a roller-fed film will typically not use frames, though frames are an option as discussed above.

Using the techniques and apparatuses described herein, uniform depositions of ±5%, and as precise as ±3% of a target amount are obtained. Such depositions can include, for example, depositions onto 4 mm diameter collection zones of amounts ranging from 2 μg to 50 mg.

In view of the low variability in dosage levels (*i.e.*, the amount of active ingredient) of unit dosage forms produced in accordance with the present teachings, such dosage forms, and the methods and apparatus by which they are made, are advantageously used for treating a unique set of disease conditions that require a well-controlled dose regimen. Such well-controlled dose regimens may be required, for example, for compounds with overlapping doses and narrow therapeutic windows. Such narrow therapeutic windows may be necessary to avoid toxic side effects, or due to changes in disease state, or as a function of the size/metabolism of the patient, or due to changes in the patient's condition. Several examples of narrow-therapeutic-window products are described below.

EXAMPLE I - Levothyroxine

Adult doses (micrograms - μg): 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300. Recommended pediatric doses (μg) for Congenital Hypothyroidism:

Age	Dose/Day	Daily Dose/Kg body wt.
0 - 6 mo.	25 - 50	8 - 10
6 - 12 mo.	50 - 75	6 - 8
1 - 5 yr.	75 - 100	5 - 6
6 - 12 yr.	100 - 150	4 - 5

EXAMPLE II – Digoxin

Adult doses (μg): 125, 250 and 500.

Patients with renal insufficiency require a smaller than usual maintenance dose of Digoxin. Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of decreased excretion of Digoxin. Newborn infants display considerable variability in their tolerance to Digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

EXAMPLE III - Warfarin

Adult doses (milligrams- mg): 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10.

EXAMPLE IV - Nitroglycerin

Adult doses (μg): 300, 400 and 600.

Additional Final Dosage Forms

As previously noted, unit dosage forms, such as unit forms **6** of FIGS. 1-5, can be used to create a variety of final dosage forms useful for different applications. In one embodiment, a final dosage form is produced by disposing one or more unit dosage forms **6** within an outer shell via well-known "blow-fill-seal" technology, as depicted in FIGS. 43a-43d.

First, a pharmaceutically-acceptable polymer **4308p** is "blown," such as with compressed gas, into mold **4302** such that polymer **4308p** remains against inner wall **4304** of mold **4302**. Upon cure, polymer **4308p** will form outer shell **4308** of a final dosage form **4310** (*see* FIG. 43d). Although depicted with a "peanut" shape, it should be understood that mold **4302** can be suitably formed to provide a final dosage form having any one of a multiplicity of desired shapes.

As illustrated in FIG. 43b, one or more unit forms **6**, as is required to obtain a desired dosage level, is introduced into mold **4302** after polymer **4308p** has cured. After introducing the desired number of unit forms **6**, and any additional fillers, *etc.*, "mouth" **4306** of mold **4302** is sealed, as depicted in FIG. 43c. Polymer **4308p**, for example, can be used to seal mouth **4306**. Mold **4302** is then opened, and final dosage form **4310** is removed, as depicted in FIG. 43d.

In another embodiment, pharmaceutical films (*e.g.*, starch-derived, cellulose-derived, polyethylene glycol-derived, *etc.*) having sufficient thickness are used as a "container" for one or more unit forms **6**. As depicted in FIG. 44a, a first film **4402** receives one or more unit forms **6** in one or more wells **4404**. Second film **4406** is placed over first film **4402** to seal the wells **4404**, as depicted in FIG. 44b. The films can then be diced to separate the wells **4404** providing a plurality of final dosage forms **4410**, as illustrated in FIG. 44c.

In a third embodiment of a final dosage form, a strip **4** is sandwiched between two films **4502** and **4504**, as depicted in FIG. 45a. The elements of strip **4** have been previously described (see FIG. 1 and the accompanying description), and include a substrate **8** and a cover layer **9**. Substrate **8** includes a plurality of depositions that have been deposited in accordance with the methods, and via the apparatus, described herein. Each deposit includes an active ingredient. The cover layer **9** includes a plurality of bubbles or bumps **12** that are aligned with the deposits on substrate **8**. A bubble **12**, an "underlying" portion of substrate **8** and an associated deposit define a unit form **6**. Strip **4** thus comprises a multiplicity of unit forms **6**.

Films **4502** and **4504** are bonded to one another, or to strip 4, thereby sandwiching unit forms **6** therebetween and creating a secondary package therefor. Information pertaining to unit forms, *etc.*, is advantageously printed or otherwise reproduced on the secondary package. The secondary package and included strip **4** can be diced producing a plurality of "postage stamp" final dosage forms **4510**, one of which is depicted in FIG. 45b. In

embodiments in which the secondary package is edible, dosage form **4510**, in its "postage stamp" form, may be ingested. In embodiments in which the secondary package is not edible, unit form **6** must be removed for administering.

In a further embodiment, a final dosage form comprising a plurality of unit forms **6** having the same or different active ingredients and capable of timed release is provided. Such final dosage forms have segregating layers that separate or segregate each of the unit forms within the final dosage form. Illustrative embodiments of such a final dosage form are depicted in FIGS. 46 and 47.

FIG. 46 depicts four unit forms **6a-6d** within final dosage form **4610**, shown in an exploded view for clarity of illustration. In a first embodiment, unit forms **6a-6d** are identical (*i.e.*, same active ingredient and same amount of said active ingredient). In a second embodiment, unit forms **6a-6d** comprise the same active ingredient, but that active ingredient is present in differing amounts. And in a third embodiment, unit forms **6a-6d** comprise different active ingredients.

Final dosage form **4610** comprises "overcoat" or "overwrap" films **4604a-4604d** that segregate unit forms **6a-6d** from one another. In illustrative final dosage form **4610** depicted in FIG. 46, each overwrap film **4604a-4604d** comprises respective "dimple" **4606a-4606d** that facilitates receipt of one of the unit forms **6a-6d**. Final dosage form **4610** can be made by layering a desired number of overwrap films (*e.g.*, overwrap films **4604a-4604d**), and sandwiching a strip (*e.g.*, strip **4**) that contains a plurality of unit forms **6** between adjacent overwrap films. The strips **4** are produced in accordance with the present teachings.

The overwrap films are aligned such that dimples on each overwrap film are aligned with one another. The unit form-containing strips are aligned with the overwrap films such that a unit form from each strip is positioned within a perimeter of a dimple of an adjacent overwrap film. The various overwrap layers and sandwiched strips are "punched" in a single operation, yielding final dosage form **4610**.

Overwrap films **4604a-4604d** may be bonded to a base film **4602** before or during the punching operation. Moving from outermost overwrap film **4604d** to innermost overwrap film **4604a**, the diameter of the dimple decreases such that the dimples "nest" in the manner in which pots in a set of cookware nest one within another. In an additional embodiment (not depicted), a second grouping of nested overwrap dimples and unit forms are disposed on a second side of base film **4602**.

In an alternate embodiment, final dosage form **4610** can be manufactured via a multi-step overwrapping operation wherein a first overwrap encapsulates a first unit form, a second overwrap film and a second unit form are then positioned over the first overwrap, *etc.* building up final dosage form **4610** layer by layer.

FIG. 47 depicts a further embodiment of a final dosage form containing multiple unit forms 6. Like final dosage form **4610**, unit forms **6a-6d** of final dosage form **4710** of FIG. 47 may be identical to one another, may comprise the same active ingredient but in different quantities, or may comprise different active ingredients.

Final dosage form **4710** can be manufactured by attaching (*e.g.*, bonding, adhering, *etc.*) a "diffusion barrier" (*e.g.*, **4704a**) to a unit form **6a** and then sequentially attaching additional unit forms (*e.g.*, **6b-6d**) and additional diffusion barriers (*e.g.*, **4704b-4704c**), seriatim. As a function of application specifics, in some embodiments, an overcoat **4706** encompasses the collection of unit forms and diffusion barriers. Similarly, in some embodiments, additional overwrap layers or diffusion barriers **4702** and **4708** are attached to the first and last unit form (*e.g.*, unit forms **6a** and **6d**).

Description of the overwrap layers and diffusion barriers, as well as additional description of the base and cover substrates, are provided in the following section.

Substrates for Specific-Delivery Dosage Forms

Utilizing the present methods and apparatus, the same active ingredient can be made as a (1) prompt-release; (2) delayed release; (3) timed release; (4) post-gastric release; or (5) colonic-release unit form by suitable selection of the base and/or cover substrates. In particular, to produce such dosage forms, the same active ingredient is deposited on a substrate or laminated with a cover layer that has the following respective properties: (1) rapidly water-soluble; (2) slowly water-soluble; (3) insoluble but water-swellable; (4) acid-insoluble but alkaline-soluble; or (5) insoluble but sensitive to degradation by anerobic attack.

Certain generalization can be made concerning desirable properties of the various substrates, overlayers and diffusion barriers previously described. Such properties, and candidate materials possessing such properties, are listed and described below.

Substrate

As previously described, the substrate serves as a deposition substrate upon which powder is electrostatically deposited. Materials suitable for use as a substrate advantageously possess the following properties: electrically resistive (minimum 5×10^{11} ohm/sq. at a relative humidity ≤ 40%); strong; dimensionally stable; low moisture uptake; insoluble (where insolubility does not pose a safety issue); optically diffuse and darkly colored; and sealable.

Candidate materials for a base substrate possessing the above-listed desirable properties include, without limitation, ethyl cellulose, cellulose acetate phthalate, water-insoluble acrylic copolymers, paper (specialty if oral approval is sought), cross-linked poly(vinyl pyrrolidinone), cross-linked gelatin, and non-woven fabric.

Example

A base substrate was produced from an aqueous dispersion of ethyl cellulose (commerically available from FMC Company of Philadelphia, PA. as Aquasol ECD). The film- formation-temperature of the as-supplied ethyl cellulose was undesirably high. Film-formation-temperature can be reduced with additives, such as, for example, a plasticizer. In one embodiment, triacetin is added to the ethyl cellulose in an amount in the range of about 15 to about 40 volume percent, and preferably between 25 and 30 volume percent. Triacetin additive produced coherent, supple films that formed at low temperatures (*e.g.*, 50° - 60° C). Table II lists the electrical properties of such films as a function of relative humidity (RH).

Table II

Electrical Properties of Films Produced from Ethyl Cellulose Dispersion Plasticized with Triacetin

	20% RH	30% RH	40% RH	60% RH
Surface Sheet Resistance, <ohm/square>:	1.0×10^{12}	7.9×10^{11}	4.1×10^{11}	1.8×10^{11}
Volume Resistivity, <ohm-cm>:	1.0×10^{12}	7.9×10^{11}	4.1×10^{11}	1.8×10^{11}

As previously described, the substrate and cover layer utilized in conjunction with the present invention are bonded to one another to form a unit dosage form. In an embodiment depicted in FIG. 48, substrate **4880** comprises a bi-layer film that includes hydrophobic layer **4882** and hydrophilic layer **4884**. Hydrophobic layer **4882** maintains high electrical resistance and mechanical stability under a wide range of conditions (*e.g.*, temperature, humidity, *etc.*). Hydrophilic layer **4884** swells or becomes "tacky" upon exposure to high humidity. Bi-layer substrate **4880** can be bonded to a cover layer by ultrasonic welding, exposure to high humidity, or directed application (*e.g.*, by ink-jet printing or micropipette) of small droplets of water.

In one embodiment, bi-layer substrate **4880** comprises an ethyl cellulose dispersion ("ECD") plasticized with triacetin as hydrophobic layer **4882** and hydroxypropyl cellulose ("HPC") as hydrophilic layer **4884**. Electrical properties of the HPC-ECD base substrate are provided below in Tables III and IV as a function of relative humidity (RH).

Table III

Electrical Properties of Multi-Layer Films Comprising HPC Type LFP Cast on ECD

Property	Surface Tested	20% RH	30% RH	40% RH	60% RH
Surf. Sht. Resistance*	HPC	1.5×10^{12}	8.0×10^{11}	5.8×10^{11}	1.4×10^{11}
Surf. Sht. Resistance	EPC	3.0×10^{12}	1.7×10^{12}	1.3×10^{12}	3.2×10^{11}
Volume Resistivity**	HPC	1.9×10^{13}	9.2×10^{13}	7.0×10^{12}	2.4×10^{12}

Table IV

Electrical Properties of Multi-Layer Films Comprising HPC Type JFNF Cast on ECD

Property	Surface Tested	20% RH	30% RH	40% RH	60% RH
Surf. Sht. Resistance*	HPC	1.0×10^{12}	4.7×10^{11}	2.3×10^{11}	1.0×10^{11}
Surf. Sht. Resistance	EPC	2.6×10^{12}	1.2×10^{12}	6.8×10^{11}	3.8×10^{11}
Volume Resistivity**	HPC	1.1×10^{12}	9.5×10^{12}	5.7×10^{12}	2.2×10^{12}

hydrophobic layer

(*<ohm/square>, **<ohm-cm>)

Other candidate materials for hydrophobic layer **4882** that are commercially-available as aqueous dispersions are cellulose acetate phthalate and water-insoluble acrylic copolymers. Additional candidates that are suitable, but require more complex processing include, without limitation, unmodified cellulose, unmodified starch, chitin and other materials previously identified as candidates for the base substrate.

Other candidate materials for hydrophilic layer **4884** that are readily available include hydroxypropylmethyl cellulose, methylcellulose, modified starches, maltodextrins, natural and synthetic gums, poly(vinyl alcohol), poly(vinyl pyrrolidinone), and the like, and hydrogels derived from these and other similar materials.

A method **4900** for forming such a bi-layer film is depicted in FIG. 49. The illustrative method involves two primary operations: casting the hydrophobic layer (step **4910**) and casting the hydrophilic layer (step **4920**). The hydrophobic layer is cast, for example, by applying a suitable material (*e.g.*, plasticized ethyl cellulose dispersion) on a casting substrate, as depicted in operation **4910a**. A smooth, poorly adherent plastic film (*e.g.*, Mylar™, stainless steel) is advantageously used as the casting substrate. The applied material is then dried under conditions of controlled temperature and humidity as per operation **4910b**. A temperature of 55°C and relative humidity of 35% have been found to be suitable for performing drying operation **4910b**. Other conditions of temperature and relative humidity may suitably be used.

The hydrophilic layer is then cast from a solution applied to the hydrophobic film in operation block **4920a**. The applied solution is dried under conditions of controlled temperature and humidity in operation **4920b**. A temperature of 28°C and relative humidity of 45% have been found to be suitable for performing drying operation **4920b**. Other conditions of temperature and relative humidity may suitably be used.

After the hydrophobic layer and the hydrophilic layer have been cast, the resulting bi-layer film is then removed from the casting substrate in a final operation **4930**. Such removal can be effected by peeling the bi-layer film from the casting substrate.

In an alternate embodiment, rather than casting the hydrophobic layer, a commerically-available pre-formed pharmaceutically-approved hydrophic film may be used. The hydrophilic layer is then cast over the hydrophobic film.

Cover Layer

As previously described, the cover layer is used in the electrostatic deposition process to cover the substrate thereby trapping the deposited active ingredient therebetween. Materials suitable for use as a cover layer advantageously possess the following properties: immediately soluble in all conditions of pH, temperature and the like; deformable to accept a range of doses; and easily dyed for color coding.

Candidate materials for a cover layer possessing the above-listed desirable properties include, without limitation, commerical hydroxypropylmethyl cellulose, methyl cellulose, hydroxypropyl cellulose, poly(vinyl pyrrolidinone), poly(vinyl alcohol), poly(ethylene oxide).

Diffusion Barrier

A diffusion barrier may be used, for example, in final dosage forms containing multiple unit dosages, such as final dosage form **4710**. Materials suitable for use as a diffusion barrier advantageously possess the following properties: swollen equally across full pH range; control diffusion of water; cross-linked water-soluble polymer; active ingredient delivery rate controllable by material thickness or by degree of cross-linking density.

Candidate materials for the diffusion barrier include, without limitation, poly(methacrylic acid), acrylic hydrogels (*e.g.*, mildly cross-linked polymers of hydroxyethyl or hydroxypropyl acrylate or methacrylate), polysaccharides (*e.g.*, starches, agar, maltodextrin, *etc.*), gums (*e.g.*, acacia, gellan, *etc.*), and carboxymethyl cellulose.

Overcoat Films

An overcoat (overwrap) film is used, for example, where a secondary packaging layer surrounds the unit forms, such as for final dosage forms **4310**, **4410**, **4510**, **4610**, and some embodiments of **4710**. Properties of the overcoat films are defined as a function of the desired characteristic (*e.g.* prompt-release; delayed release; post-gastric release, *etc.*) of the final dosage form.

In particular, for release in the stomach, the overcoat film is advantageously acid soluble. Suitable acid-soluble materials include, without limitation, poly(vinyl pyridine), and amine-substituted acrylic copolymers. For release in the small intestine, the overcoat film is

alkaline soluble and/or enzyme erodable. Suitable alkaline-soluble materials include, without limitation, carboxyl-substituted acrylic copolymers and polymeric derivatives of alginic acid. Suitable enzyme-erodable materials include, without limitation, protein (*e.g.*, casein, gluten, albumin, *etc.*), lipid, starch, polylactide and poly(lactide-co-glycolide).

For colonic release, the overcoat film is advantageously universally but slowly water soluble and digestible by anerobic bacteria. Suitable water-soluble materials include, without limitation, ultra-high molecular weight poly(ethylene oxide), high molecular weight poly(ethylene glycol)s blended with poly(vinyl pyrrolidinone) or poly(vinyl alcohol), shellac, fully (≥ 98%) or slightly (≤ 25%) hydrolyzed poly(vinly alcohol), and poly(styrene-co-maleic anhydride), high molecular weight acrylate and methacrylate copolymers containing significant amounts of acidic monomers such as acrylic acid and methacrylic acid.

Adhesives

Adhesives are used, in some embodiments, for bonding the substrate and cover layer together, and for bonding various overcoat/overwrap layers to other layers. For buccal, gingival and nasal locations, the adhesive advantageously provides good adhesion and is non-toxic. Suitable adhesives include, without limitation, synthetic rubber, acrylic pressure-sensitive adhesives, dental temporary, and maltodextrin. For dermal applications, the adhesive advantageously provides good adhesion and is non-allergenic. A suitable adhesive is the type used for adhesive bandages. For vaginal and rectal applications, the adhesive advantageously exhibits poor adhesion and is non-allergenic. A suitable adhesive is a "swell-in-place" material such as polysaccharide.

All patents and patent applications cited in this specification are incorporated herein by reference in their entirety. Any patent application to which this application claims priority is also incorporated herein by reference in its entirety.

It will be understood by those skilled in the art that variations in the illustrated devices and methods may suitably be used in conjunction with the present invention and that the invention may be practiced otherwise than as specifically described. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the claims that follow.

We Claim:

1. A dry powder deposition apparatus for depositing powder on a substrate comprising:

an electrostatic chuck having one or more collection zones, each of which collection zones is operable, in conjunction with a bias source, to generate a powder-attracting electrostatic field;

a substrate that is detachably engaged to the electrostatic chuck and overlies the collection zones;

a charged powder delivery apparatus for directing charged powder to the substrate; and

an optical detection device for obtaining data indicative of an amount of powder deposited at each collection zone.

2. The apparatus of claim 1, further comprising a transport element operable to move the electrostatic chuck to an input/output station to engage said substrate, and to a deposition station to receive charged powder, and to a dose measurement station for acquisition of measurement data by said optical detection device.

3. The apparatus of claim 1, further comprising a frame that receives said substrate, wherein the frame has a first alignment feature.

4. The apparatus of claim 1, further comprising:

a deposition sensor for obtaining data indicative of an amount of deposited powder; and

a processor operable to receive the data indicative of the amount of deposited powder and further operable, in conjunction with a controller, to adjust deposition parameters responsive to the received data.

5. The apparatus of claim 4, wherein the processor is further operable to receive data indicative of the amount of deposited powder from the optical detection device.

6. A dry powder deposition apparatus for depositing powder on a substrate comprising:

a platform having:

an input/output station for storing said substrate;

a deposition station at which powder is electrostatically deposited on said substrate;

a dose measurement station for obtaining data indicative of an amount of powder deposited on said substrate; and

a lamination station at which a cover layer is laminated to said substrate after powder deposition.

7. The apparatus of claim 6, further comprising:

a first transport element that is operable to engage said substrate at said input/output station and further operable to transport said substrate to the deposition, dose measurement and lamination stations.

8. The apparatus of claim 7, further comprising:

a second transport element comprising a bonding head that is operable to permanently join said cover layer to said substrate at the lamination station.

9. The apparatus of claim 7, further comprising:

an alignment station for aligning said substrate to said first transport element.

10. The apparatus of claim 7, further comprising:

a receiver connected to said first transport element; and

an electrostatic chuck having a plurality of collection zones, each of which zones is operable, in conjunction with a source of bias, to generate an electromagnetic field, wherein said electrostatic chuck is detachably engaged to said receiver.

11. The apparatus of claim 10, and further wherein said receiver comprises electronics for controlling operation of the electrostatic chuck.

12. The apparatus of claim 6, and further comprising a powder feed apparatus that delivers the powder to said deposition station.

13. The apparatus of claim 12, wherein the powder feed apparatus comprises:
a tube for delivering powder towards said deposition station.

14. The apparatus of claim 13, further comprising a mechanical device that draws powder away from a feed hopper.

15. The apparatus of claim 14, further comprising at least one of:
a venturi feeder valve having a venturi well, the venturi feeder valve operable, in conjunction with a flow of gas, to pull said powder from said mechanical device and deliver the powder to said tube, wherein the flow of gas is further operable to propel the powder through the tube, or
a gas source for directing gas towards the outlet of said mechanical device to deagglomerate said powder and propel the powder through said tube.

16. The apparatus of claim 15, wherein the venturi well is physically arranged to pass powder from said mechanical device to said tube in a substantially straight path.

17. The apparatus of claim 13, further comprising:
a drum for temporary storage of said powder;
a movable belt that receives said powder from said drum; and
means for removing said powder off said movable belt; and
means for receiving said removed powder and directing it towards said tube.

18. The apparatus of claim 13, further comprising a baffle at an outlet of said tube for enhancing uniformity of a cloud of said powder directed towards said deposition station.

19. The apparatus of claim 13, further comprising a powder trap that recovers power that is not electrostatically deposited at said deposition station.

20. The apparatus of claim 6 further comprising walls that isolate said platform and said first transport element from an ambient environment.

21. An apparatus comprising:

deposition means for electrostatically depositing an active ingredient at discrete locations on a substrate; and

measuring means for nondestructively measuring an amount of said active ingredient deposited at said discrete locations.

22. The apparatus of claim 21, and further comprising:

lamination means for bonding a cover layer to said substrate, wherein said lamination means produces bonds that individually surround the active ingredient deposited at each of said discrete locations.

23. The apparatus of claims 21 or 22, and further comprising:

alignment means for facilitating the deposition of said active ingredient at each of said discrete locations and for facilitating the measurement of said amount of active ingredient deposited at each of said discrete locations.

24. The apparatus of claims 21, 22 or 23, and further comprising:

means for storing said substrate.

25. The apparatus of any one of claims 21-24, and further comprising:

transport means for transporting said substrate to said deposition means and to said measurement means.

26. The apparatus of any one of claims 21-25, and further comprising:

sensor means for monitoring the electrostatic deposition of the active ingredient.

27. The apparatus of claim 26, and further comprising:

processor means and controller means for receiving input from said sensor means, analyzing said received input, and controlling said deposition means responsive to said analysis.

28. The apparatus of claim 21, wherein said measuring means comprises a diffuse reflection optical detection device.

29. The apparatus of claim 21, wherein said measuring means comprises an optical profilometer.

30. The apparatus of claim 21, wherein said measuring means comprises an integrated diffuse reflectance and profilometry device.

Product claims

31. A product comprising a pharmaceutical or diagnostic unit form, the unit form comprising:

a substrate comprising a first polymer;

a deposit, including an active ingredient, disposed on a first surface of said substrate; and

a cover layer comprising a second polymer, wherein said cover layer covers the deposit and is joined to said first surface of said substrate by a bond that encircles the deposit.

32. The product of claim 31, comprising a plurality of unit forms, said plurality of unit forms comprising plural deposits disposed on said first surface of said substrate, wherein the plural deposits are covered by said cover layer.

33. The product of claim 32, wherein said active ingredient is present in the unit forms in an amount that does not vary from a target amount by more than about 5 weight percent.

34. The product of claim 32, wherein said substrate comprises a planar film.

35. The product of claim 32, wherein said cover layer comprises a planar film.

36. The product of claim 34, wherein said cover layer has a shape comprising a plurality of semi-spherical bubbles, wherein each deposit is disposed within a perimeter of one of said semi-spherical bubbles.

37. The product of claim 35, wherein said substrate has a shape comprising a plurality of semi-spherical bubbles, wherein each deposit is disposed within a perimeter of one of said semi-spherical bubbles.

38. The product according to any one of claims 31-37, wherein the one or more deposits have a shape that is substantially circular and has a size in the range of about 3 millimeters to about 10 millimeters.

39. The product according to any one of claims 31-38, wherein said first and said second polymer are the same.

40. The product according to any one of the claims 31-39, wherein said substrate and said cover layer are ingestible.

41. The product according to any one of the claims 31-38, wherein said substrate is electrically resistive and has low moisture uptake.

42. The product according to claim 41, wherein said substrate is insoluble and is optically diffuse.

43. The product according to claim 41, wherein said substrate is soluble and is transparent.

44. The product according to any one of the claims 31-38 and 40-43, wherein said substrate is selected from the group consisting of ethyl cellulose, cellulose acetate phthalate, water-insoluble acrylic copolymers, paper, cross-linked poly(vinyl pyrrolidinone), cross-linked gelatin, non-woven fabric, soy bean protein, rice protein and whey protein.

45. The product according to any one of the claims 31-44, wherein said substrate comprises an additive to reduce film-formation-temperature.

46. The product according to claim 45, wherein said additive is a plasticizer.

47. The product according to claim 46, wherein said substrate comprises ethyl cellulose, and said plasticizer is triacetin.

48. The product according to any one of the claims 31-38, wherein said substrate comprises a bi-layer film.

49. The product according to claim 48, wherein said bi-layer film comprises a hydrophobic layer and a hydrophilic layer.

50. The product according to claim 49, wherein said hydrophobic layer comprises a material selected from the group consisting of ethyl cellulose dispersion, cellulose acetate phthalate dispersion and water-insoluble acrylic copolymer dispersions.

51. The product according to claim 49, wherein said hydrophilic layer comprises a material selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, modified starches, maltodextrins, natural and synthetic gums, poly(vinyl alcohol), poly(vinyl pyrrolidinone), and hydrogels derived therefrom.

52. The product according to any one of the claims 31-38 and 45-49, wherein said cover substrate is insoluble at a specific pH and a specific temperature.

53. The product according to any one of the claims 31-38 and 45-49, wherein said cover substrate is selected from the group consisting of hydroxypropylmethyl cellulose, methyl cellulose, hydroxypropyl cellulose, poly(vinyl pyrrolidinone), poly(vinyl alcohol), poly(ethylene oxide).

54. The product according to any one of the claims 31-53, wherein the product is a final dosage form, said product further comprising a first and second overlayer that are bonded together, wherein said unit form is disposed between said first and second overlayers.

55. The product according to claim 54, wherein product information appears on at least one of said first and second overlayers.

56. A product comprising:

a plurality of pharmaceutical unit forms, each unit form comprising:

a substrate comprising a first polymer;

a deposit comprising an active ingredient, the deposit disposed on a first surface of said substrate; and

a cover layer comprising a second polymer, the cover layer covering the deposit and joined to the first surface of said substrate by a bond that encircles the deposit;

a plurality of segregating layers, wherein each segregating layer segregates one of said unit forms from at least one adjacent unit form.

57. The product of claim 56, wherein said segregating layers are overwrap films that include a dimple for receiving a unit form.

58. The product of claim 57, wherein said segregating layers are arranged in nested fashion from an innermost overwrap having a dimple with a smallest diameter, to an outermost overwrap having a dimple with a largest diameter.

59. The product of claim 56, wherein said segregating layers are diffusion barriers that join adjacent stacked unit forms.

60. The product of claim 59, further comprising an overcoat that covers said unit forms and said diffusion barriers.

61. The product according to any one of the claims 56-60, wherein said unit forms are identical.

62. The product according to any one of the claims 56-60, wherein said unit forms comprise the same active ingredient, but said active ingredient is present in differing amounts in at least some of said unit forms.

63. The product according to any one of the claims 56-60, wherein at least some of the unit forms comprise a different active ingredient.

64. The product according to any one of the claims 57, 58 and 60, wherein said overcoat is acid soluble.

65. The product according to claim 64, wherein said overcoat is selected from the group consisting of poly(vinyl pyridine) and amine-substituted acrylic copolymers.

66. The product according to any one of the claims 57, 58 and 60, wherein said overcoat is alkaline soluble.

67. The product according to claim 66, wherein said overcoat is selected from the group consisting of carboxyl-substituted acrylic copolymers and polymeric derivatives of alginic acid.

68. The product according to any one of the claims 57, 58 and 60, wherein said overcoat is enzyme erodable.

69. The product according to claim 68, wherein said overcoat is selected from the group consisting of protein, lipid, starch, polylactide and poly(lactide-co-glycolide).

70. The product according to any one of the claims 57, 58 and 60, wherein said overcoat is slowly water-soluble.

71. The product according to claim 70, wherein said overcoat is selected from the group consisting of ultra-high molecular weight poly(ehtylene oxide), high molecular weight poly(ethylene glycol)s blended with poly(vinyl pyrrolidinone) or poly(vinyl alcohol), shellac, 98% or greater hydrolyzed poly(vinly alcohol), 25% or less hydrolyzed poly(vinly alcohol), poly(styrene-co-maleic anhydride), and high molecular weight acrylate and methacrylate copolymers containing acidic monomers.

72. The product according to any one of the claims 59 and 60, wherein said diffusion barrier comprises a material that swells equally as a function of pH and is able to control diffusion of water.

73. The product according to claim 72, wherein said diffusion barrier comprises a material that is a cross-linked water-soluble polymer.

74. The product according to any one of the claims 72 and 73, wherein said diffusion barrier is selected from the group consisting of poly(methacrylic acid), acrylic hydrogels, polysaccharides, gums, and carboxymethyl cellulose.

75. A product comprising:

a substrate having a plurality of deposits comprising an active ingredient, the deposits being disposed on discrete regions of a first surface of said substrate and being formed by:

generating an electrostatic force at said discrete regions, and

directing a cloud of charged powder towards said first surface of said substrate; and

a cover layer that overlies the plurality of depositions and is joined to the first surface of said substrate by bonds that individually encircle each of said depositions.

76. The product of claim 75, wherein said cover layer has a planar form that includes a plurality of concavities, each concavity overlying a deposit and sealed individually.

FIG 1

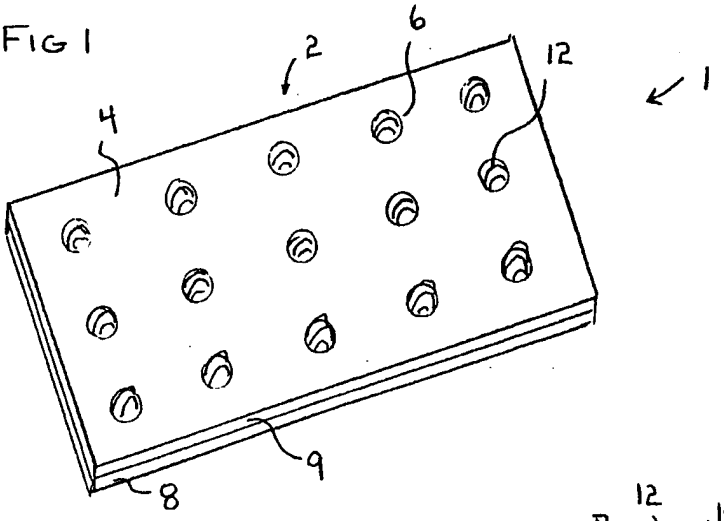


FIG. 3

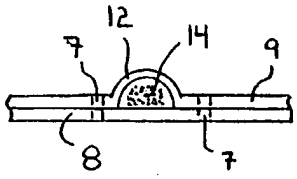
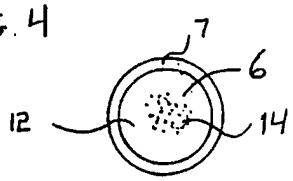


FIG. 4



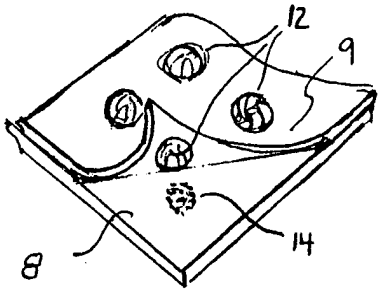


FIG. 2

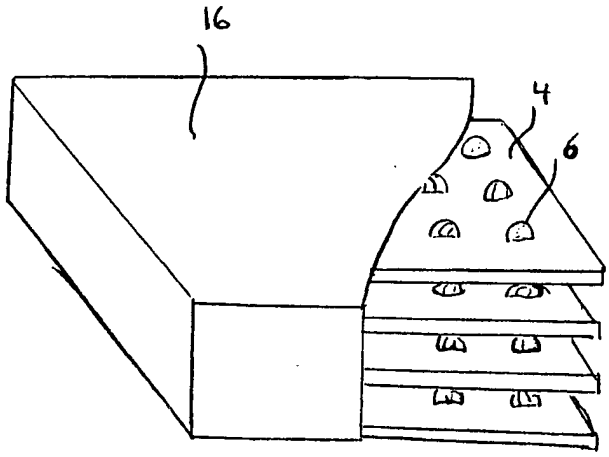
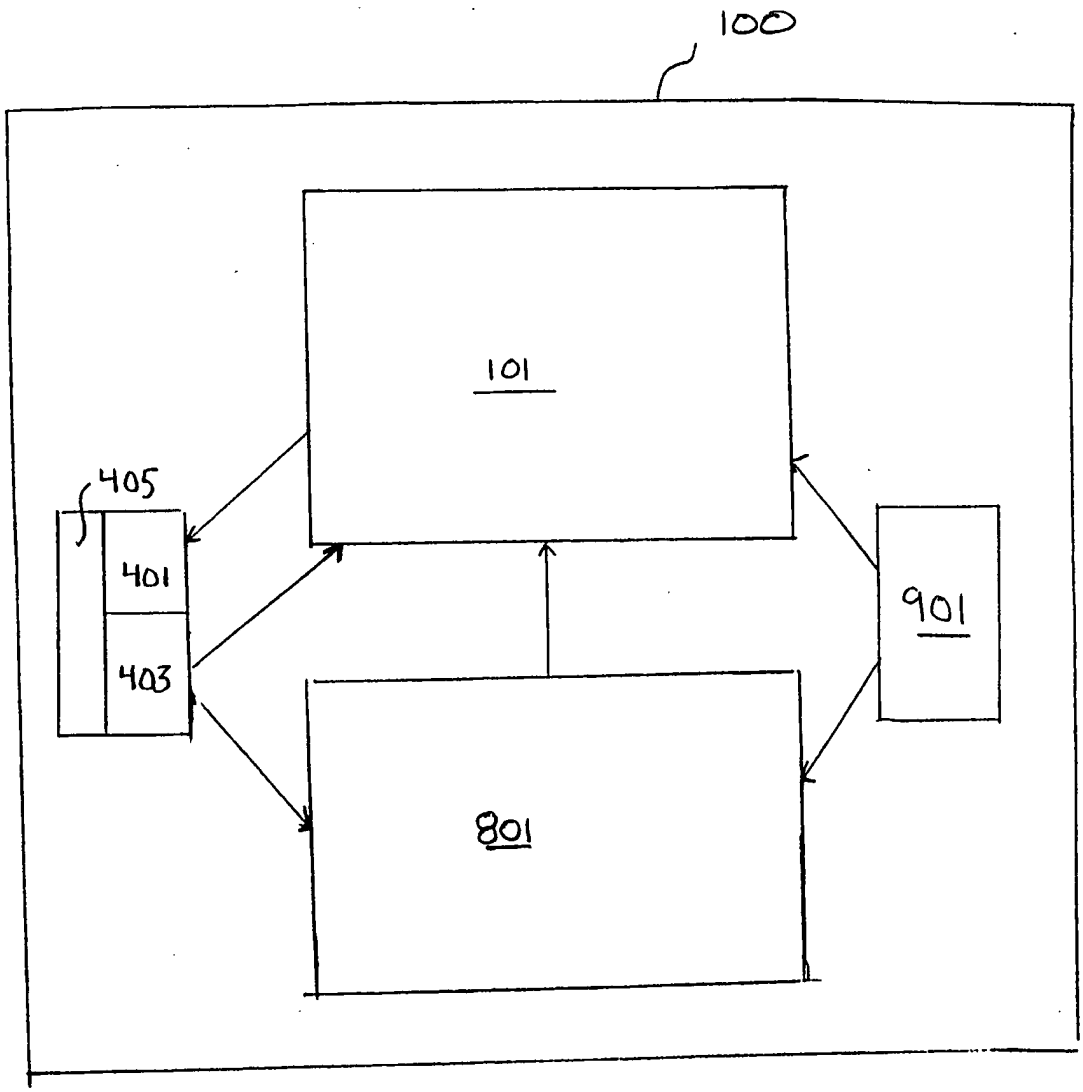


FIG. 5

FIG. 6



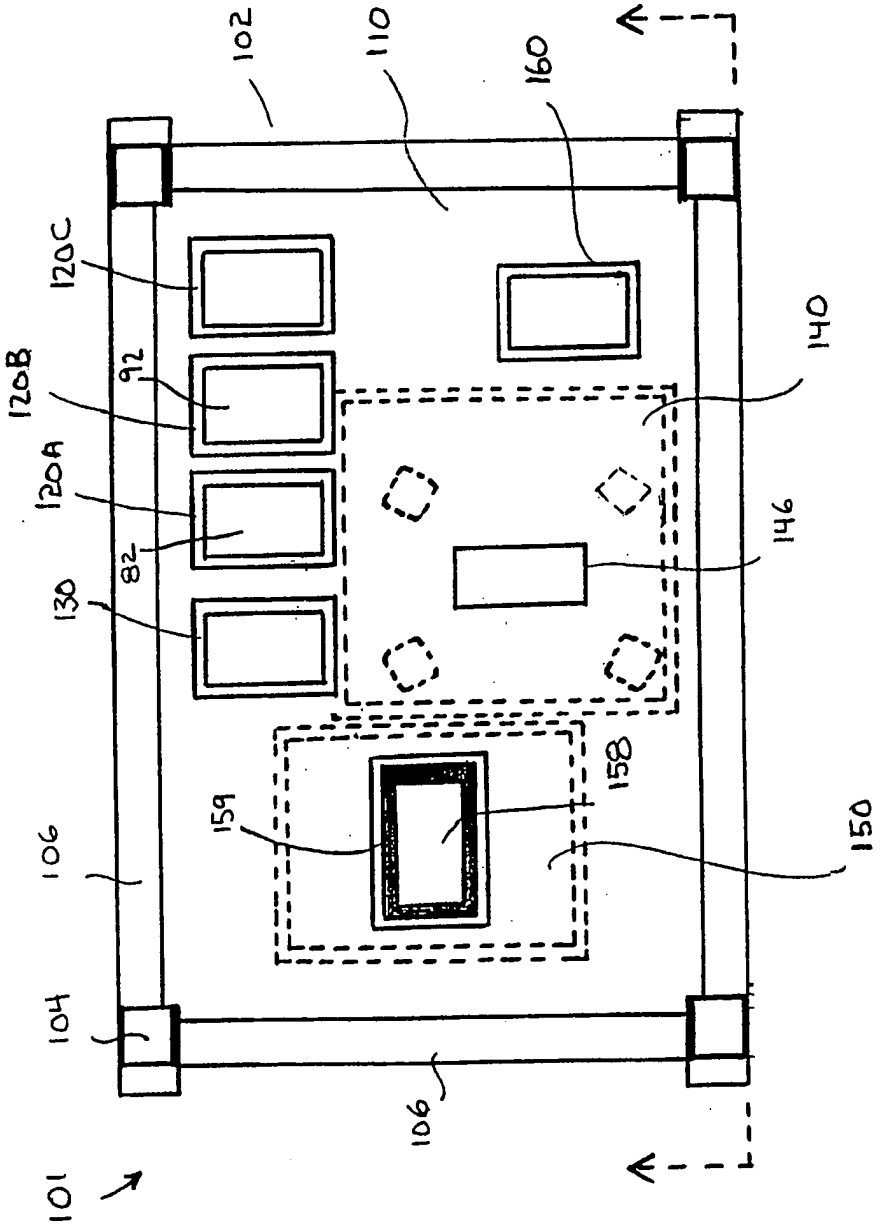

102
110
160
120C
120B
92
120A
82
130
140
146
158
159
150
106
104
106
101

FIG. 7

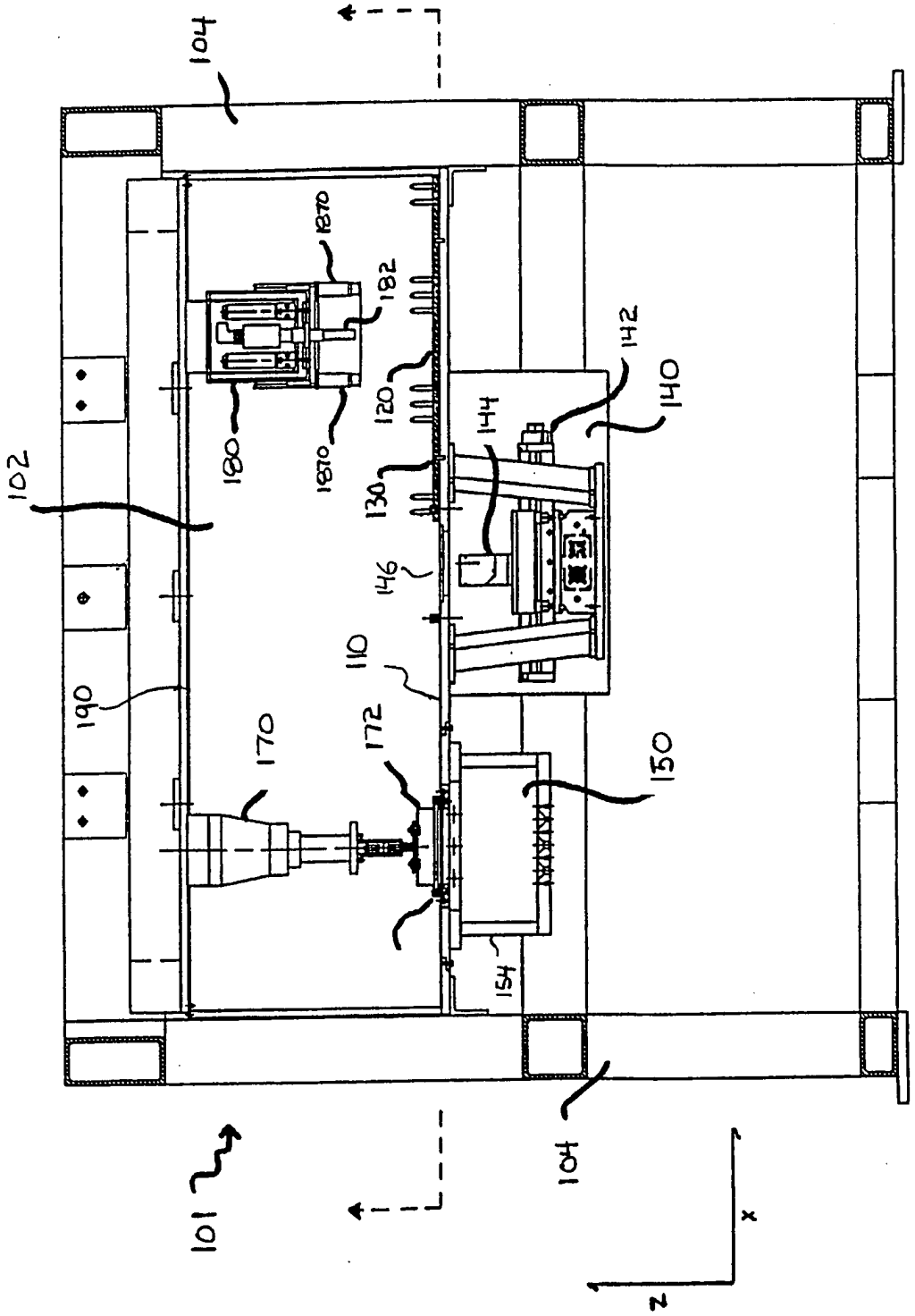

101
104
102
190
110
130
120
182
180
180a
180a
142
140
144
146
170
172
150
154
x
z

FIG. 8

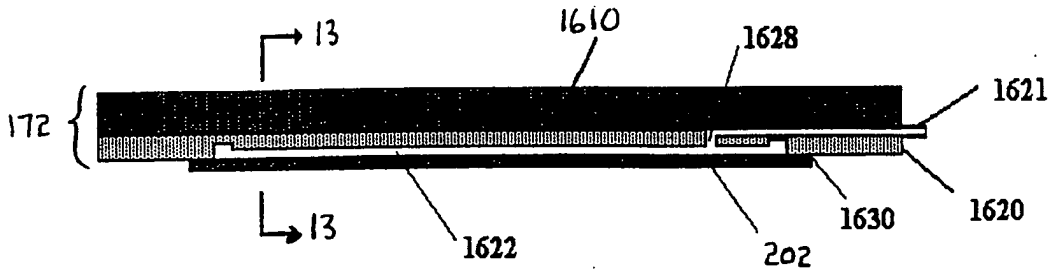

13
1610
1628
1621
172
13
1622
202
1630
1620

FIG. 9

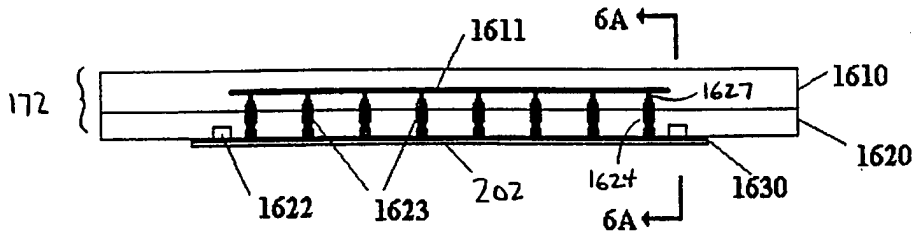

1611
6A
1610
172
1627
1620
1622
1623
202
1624
1630
6A

FIG. 13

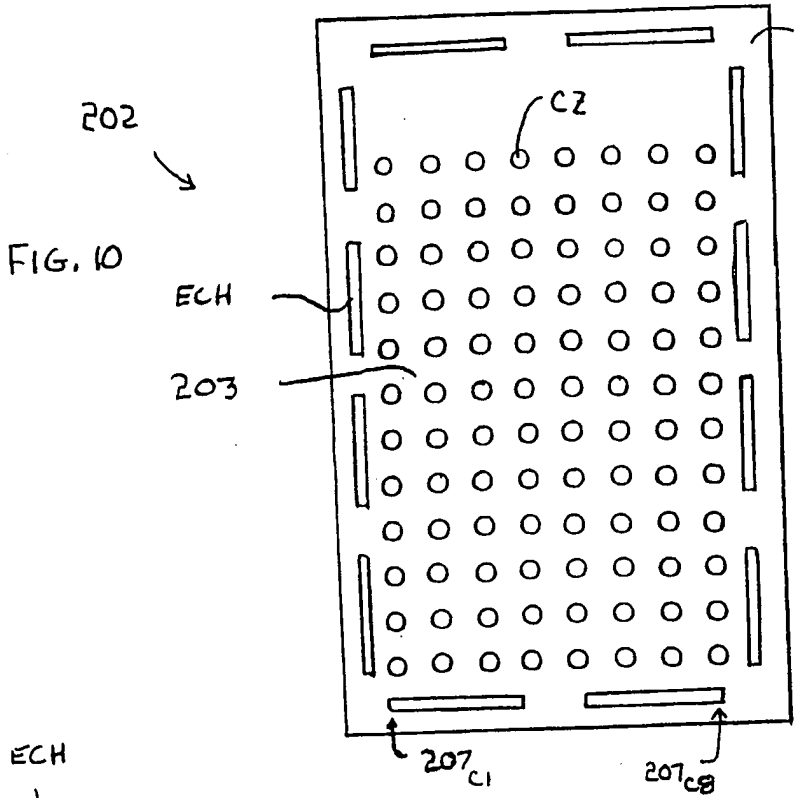


FIG. 10

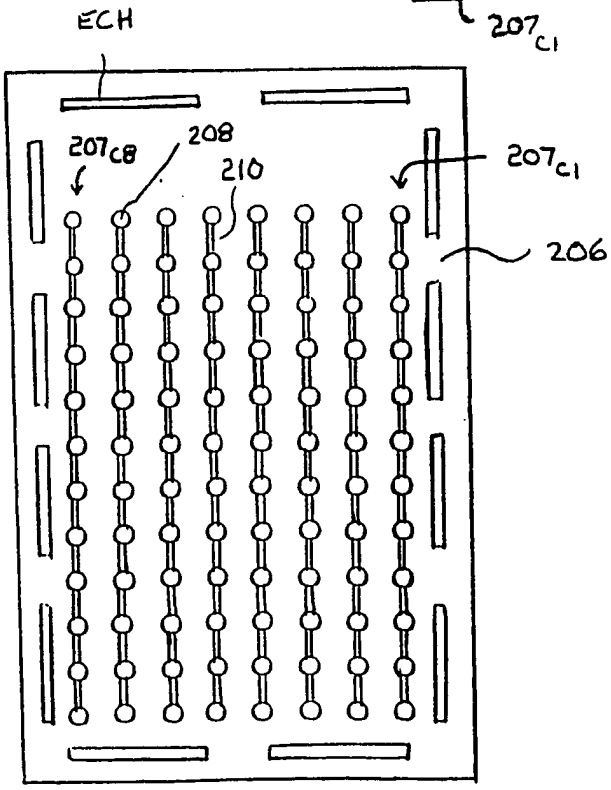


FIG. 11

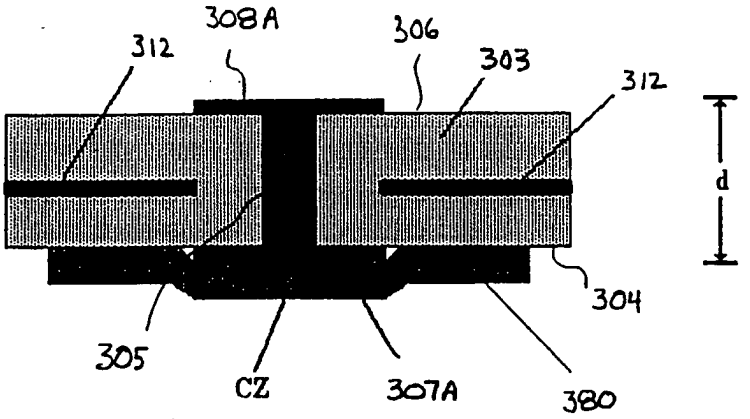


FIG 12a

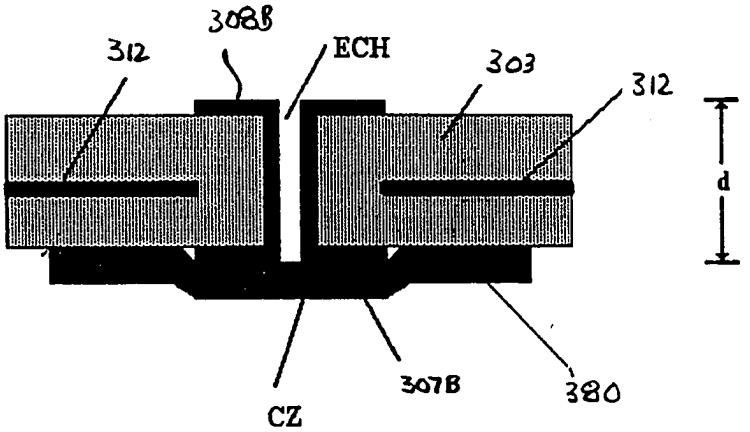


FIG 12b

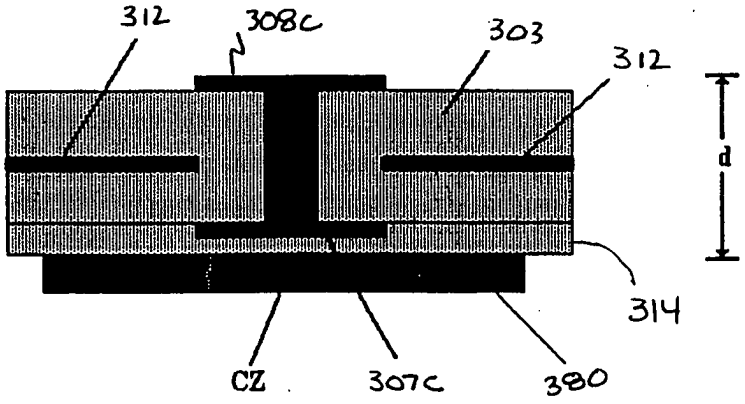


FIG 12c

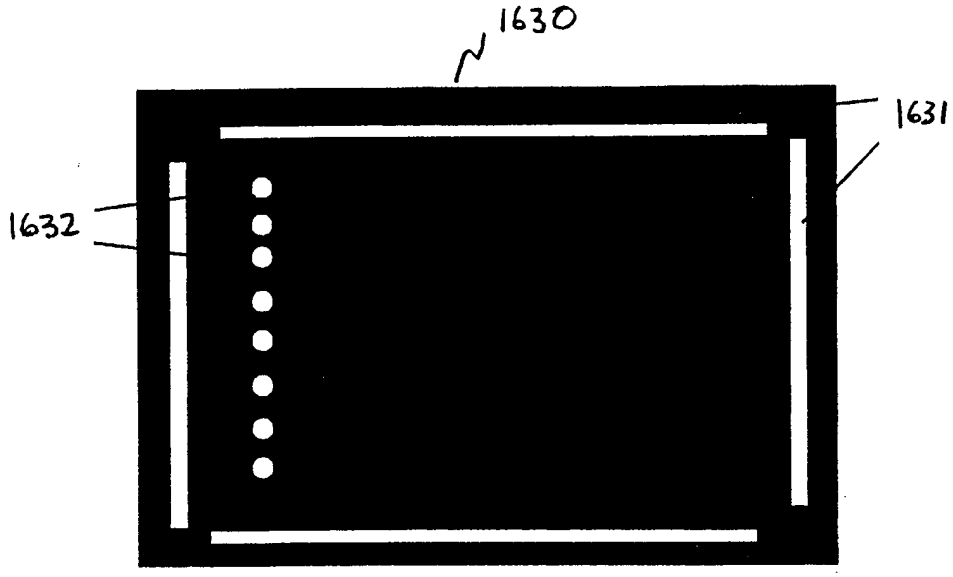


FIG. 15

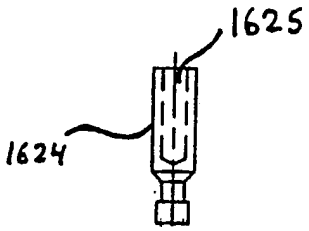


FIG 14

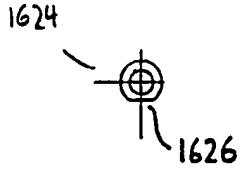


FIG. 16

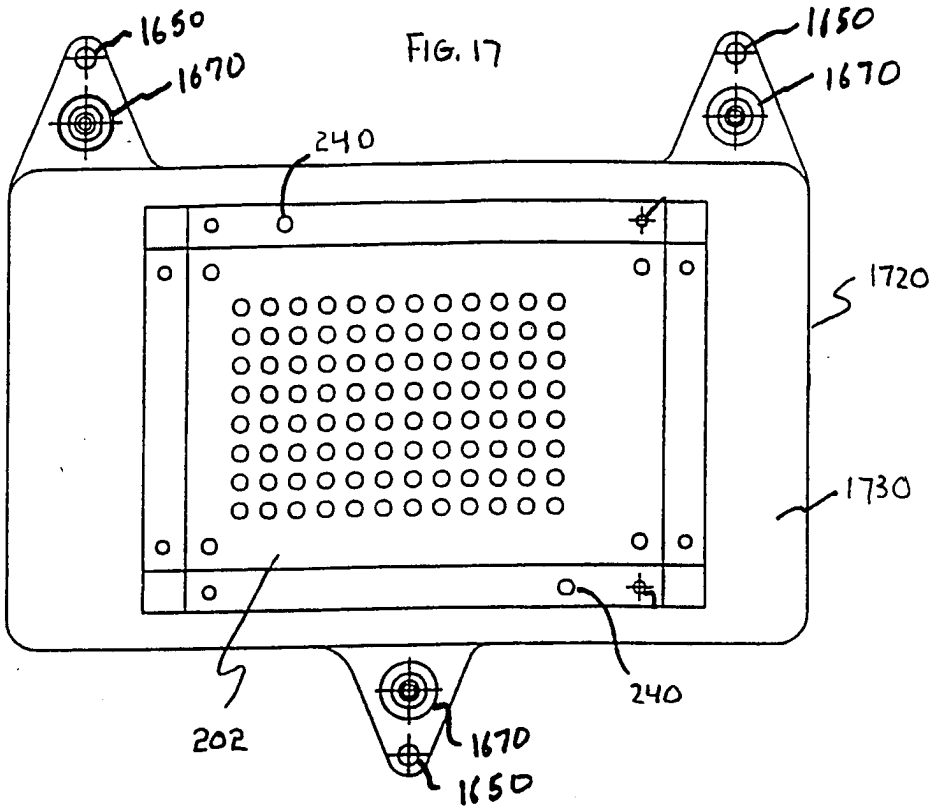

1650
1670
1150
1670
240
1720
1730
240
202
1670
1650

FIG. 17

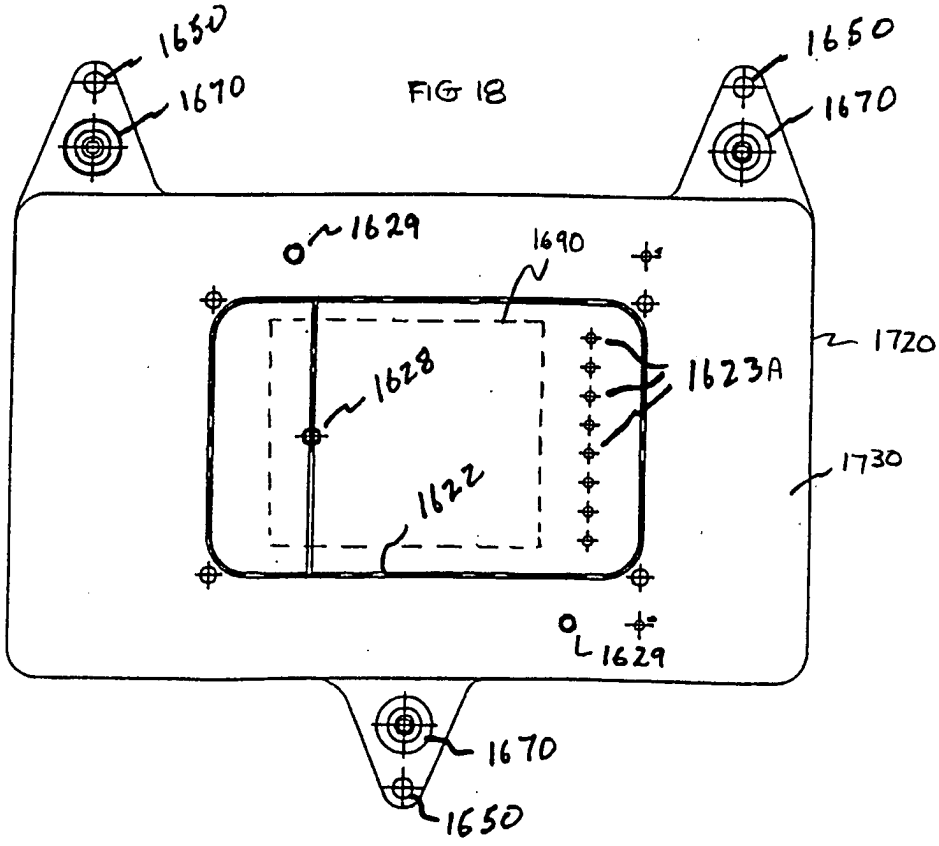

1650
1670
1650
1670
1629
1690
1720
1628
1623A
1730
1622
1629
1670
1650

FIG 18

FIG. 19

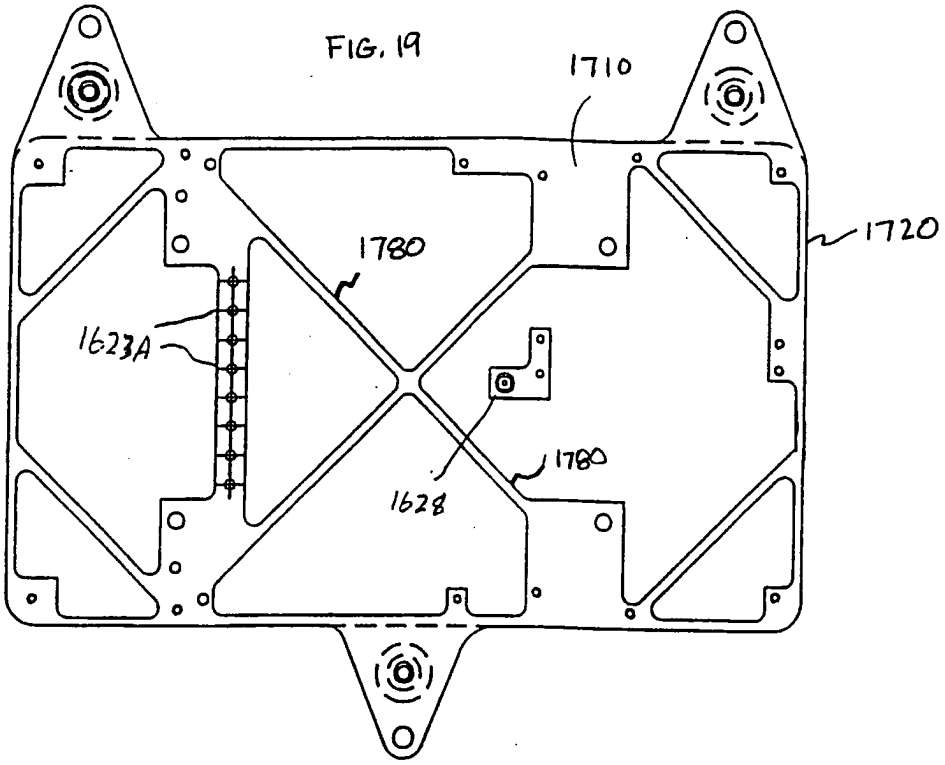

1710
1720
1780
1623A
1628
1780

FIG. 20

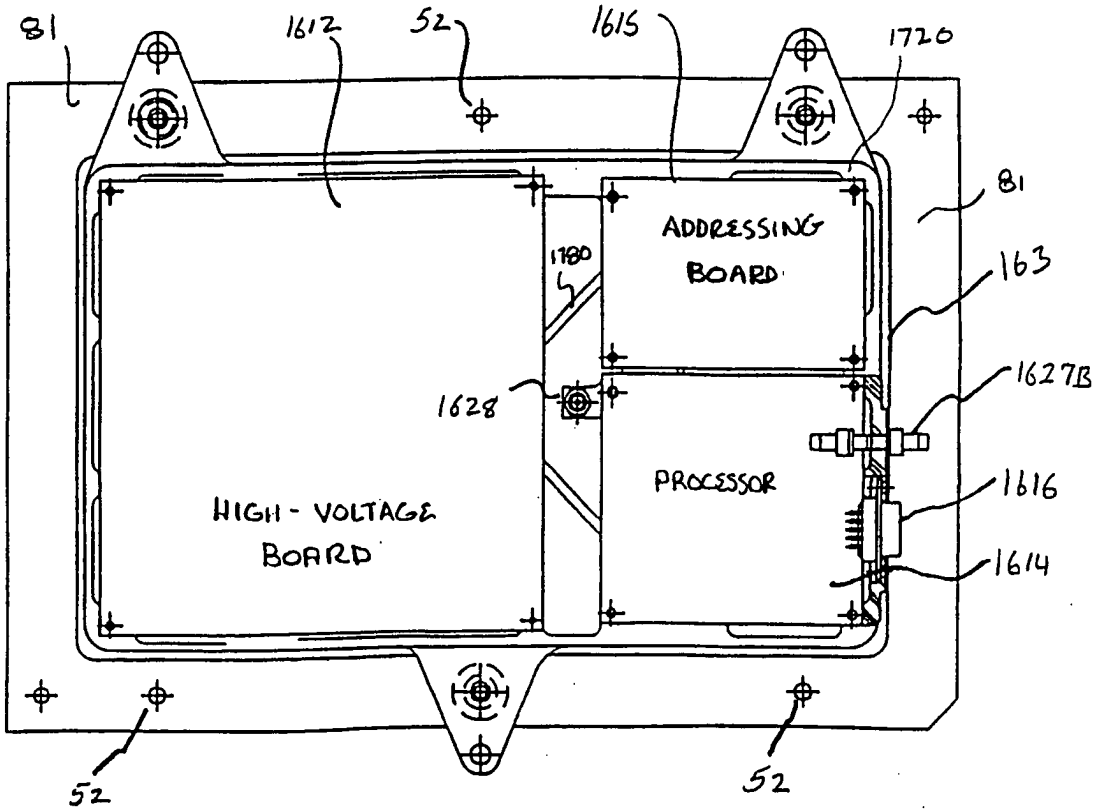

81
1612
52
1615
1720
81
ADDRESSING BOARD
1780
163
1627B
1628
PROCESSOR
1616
1614
HIGH - VOLTAGE BOARD
52
52

FIG. 21

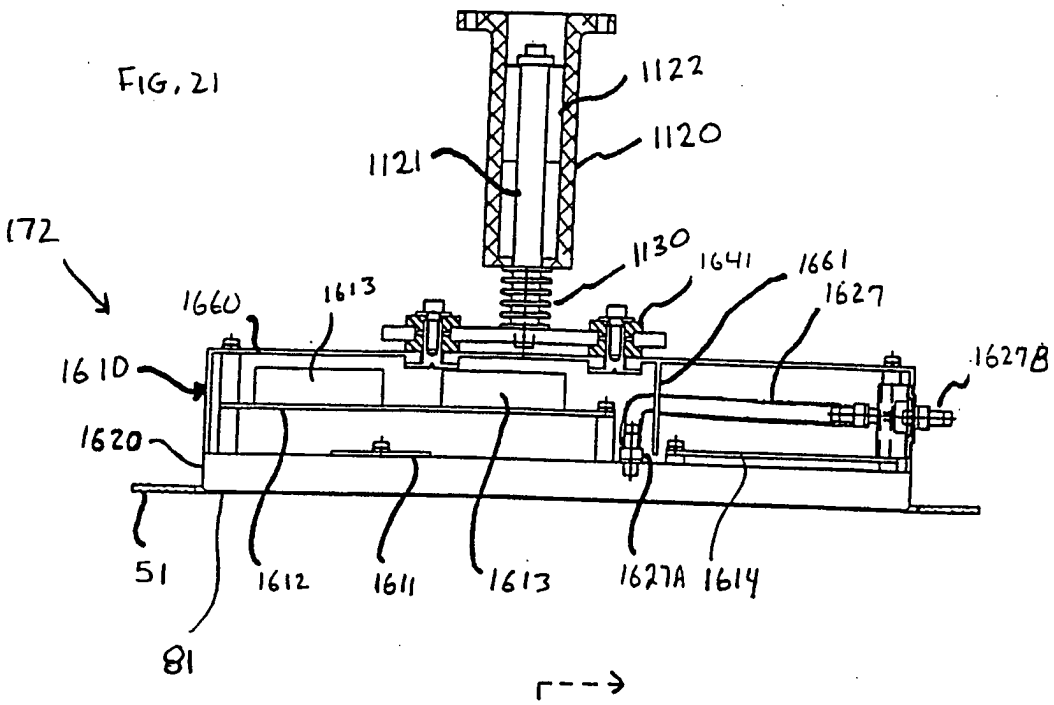

172
1122
1120
1121
1130
1641
1661
1627
1660
1613
1610
1627B
1620
51
1612
1611
1613
1627A
1614
81

FIG. 22

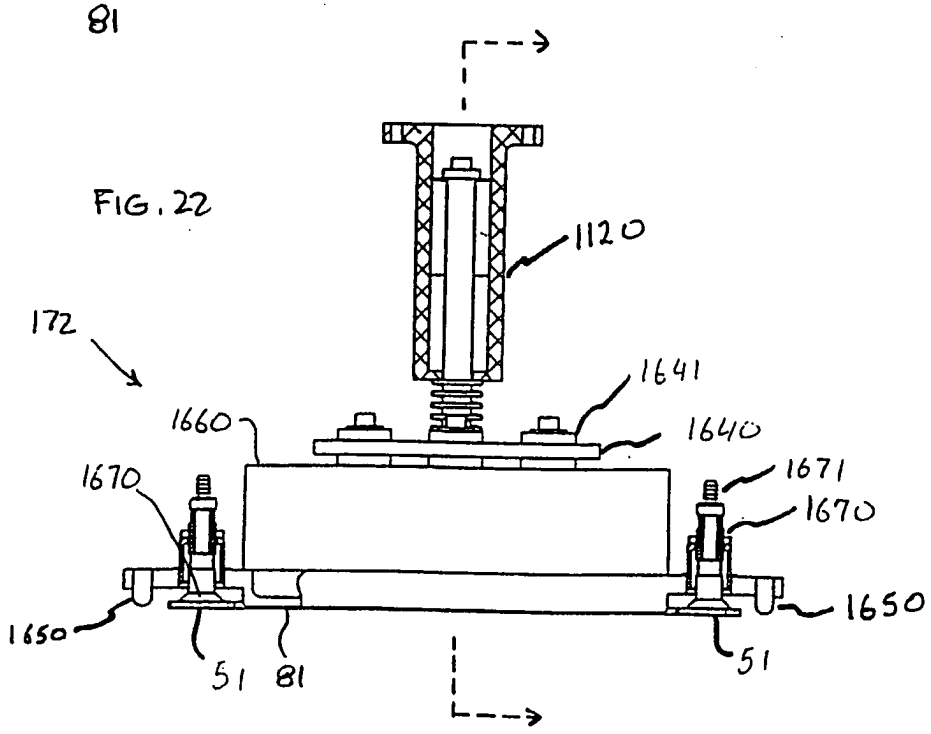

1120
172
1641
1660
1640
1671
1670
1670
1650
1650
51
81
51

FIG. 23

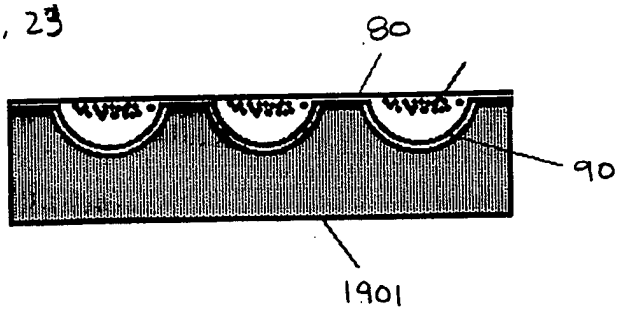

80
90
1901

FIG. 24

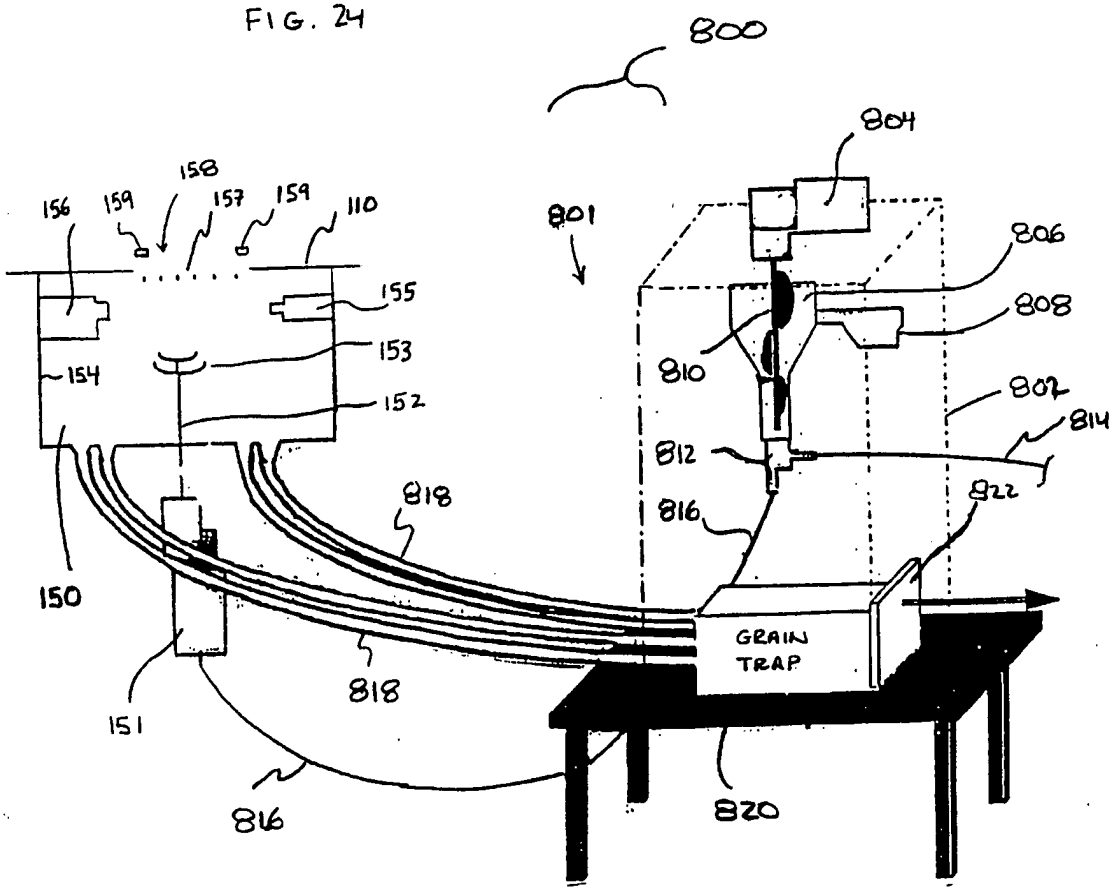
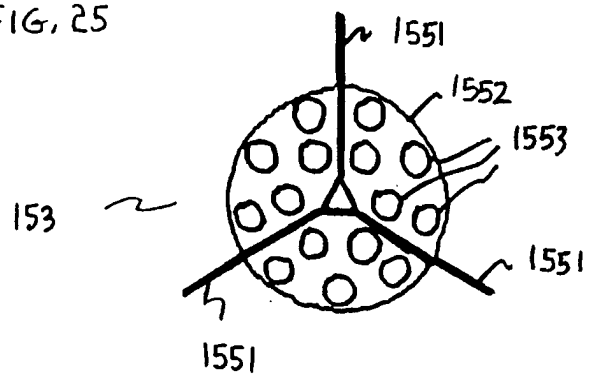

800
804
801
806
808
810
807
814
812
816
822
818
158
156
159
157
159
110
155
153
154
152
150
151
818
816
820
GRAIN TRAP

FIG. 25



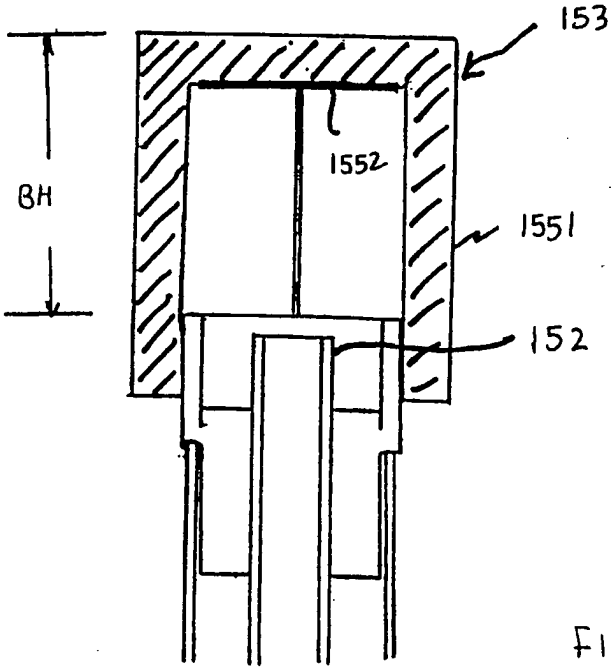


FIG. 26

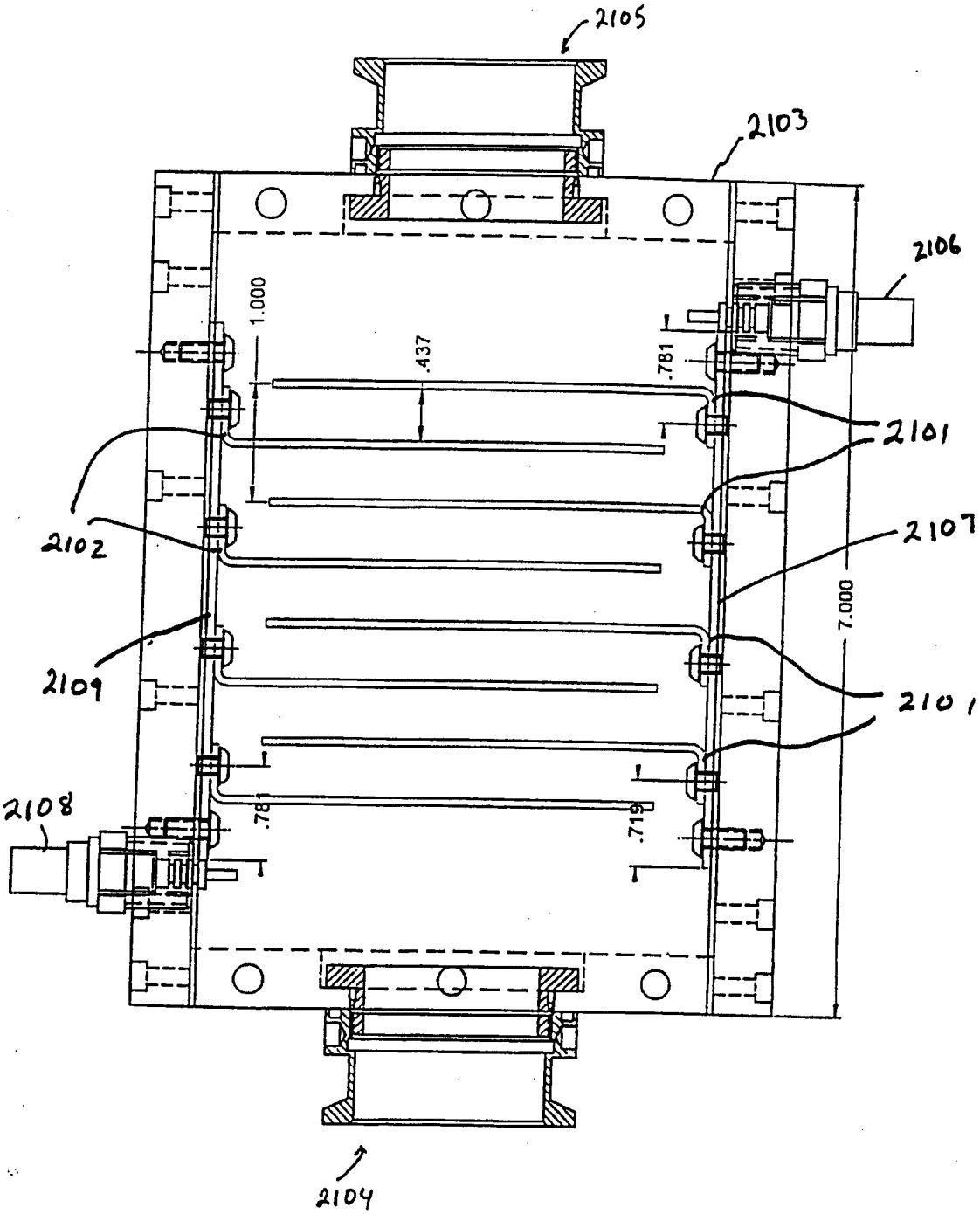
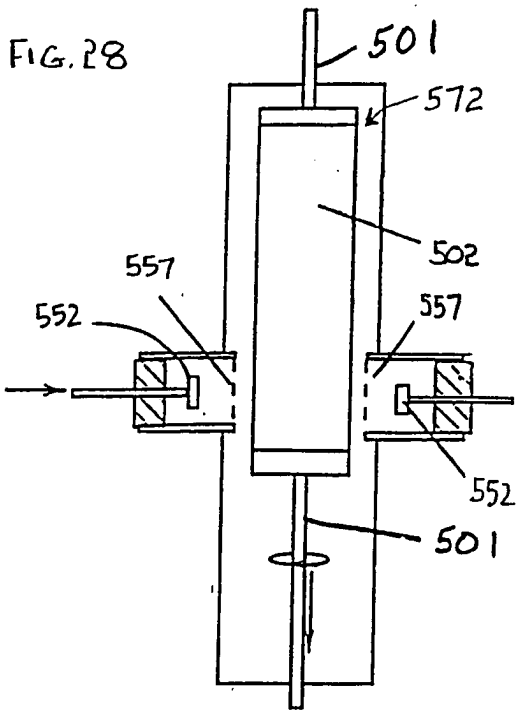

2105
2103
2106
1.000
.437
.781
2101
2102
2107
7.000
2109
2101
2108
.781
.719
2104

FIG. 27

FIG. 28



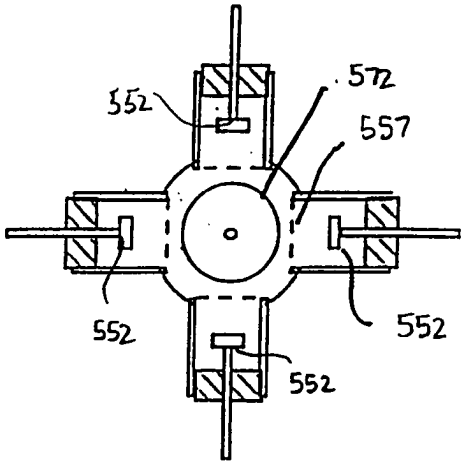
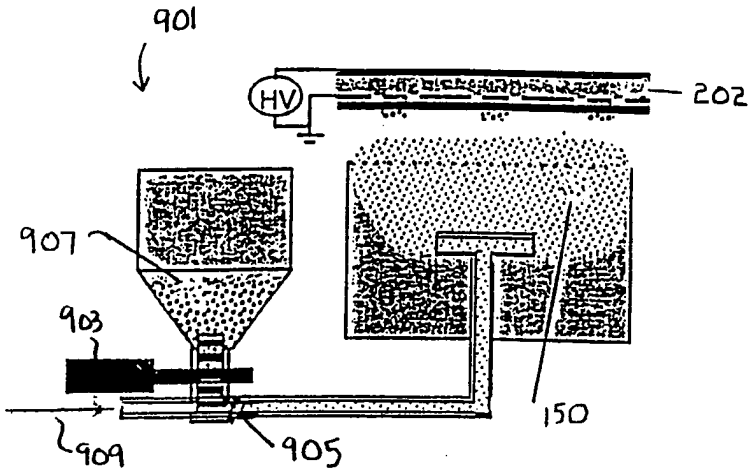


FIG. 29

FIG. 30



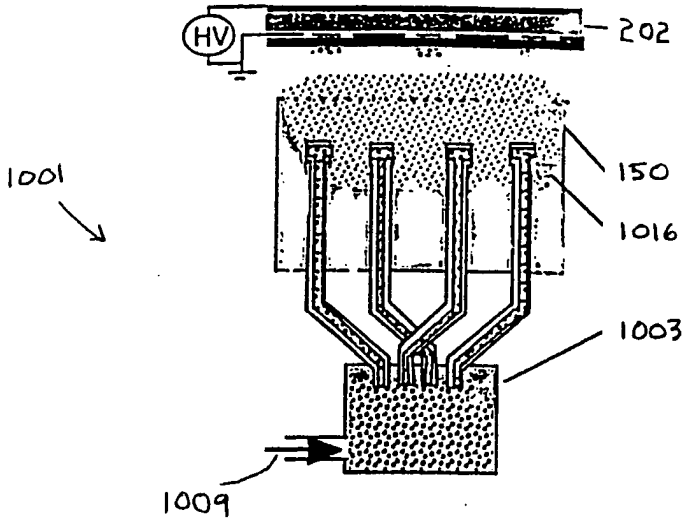


FIG. 31

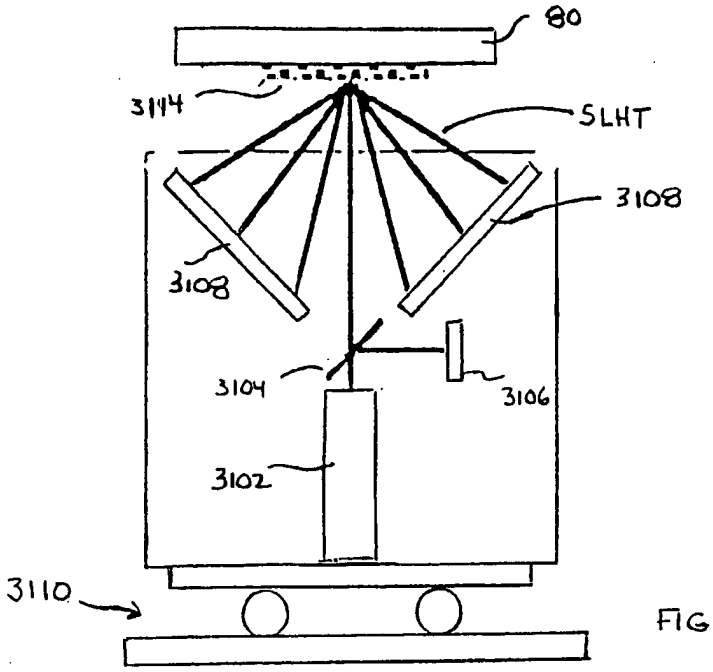

80
3114
SLHT
3108
3108
3104
3106
3102
3110

FIG. 32

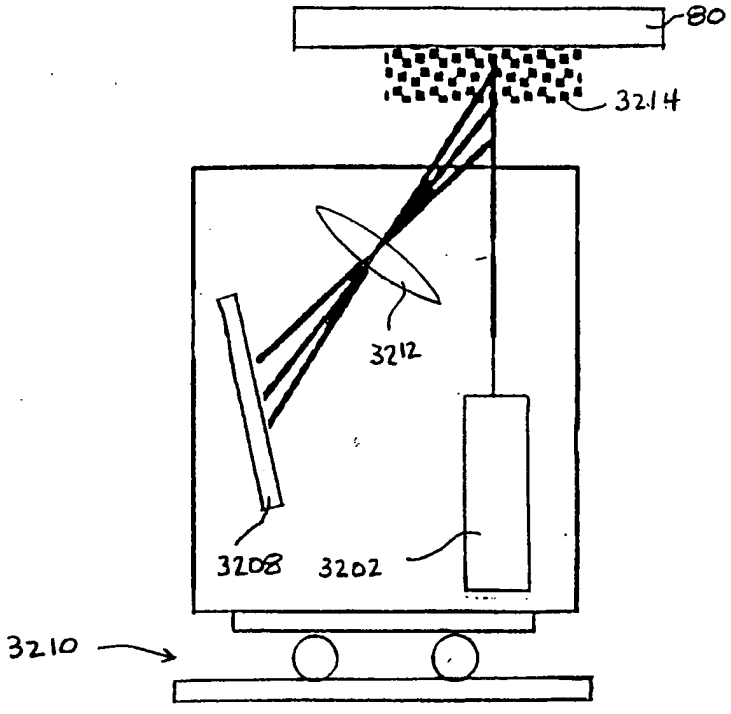

80
3214
3212
3208
3202
3210

FIG. 33

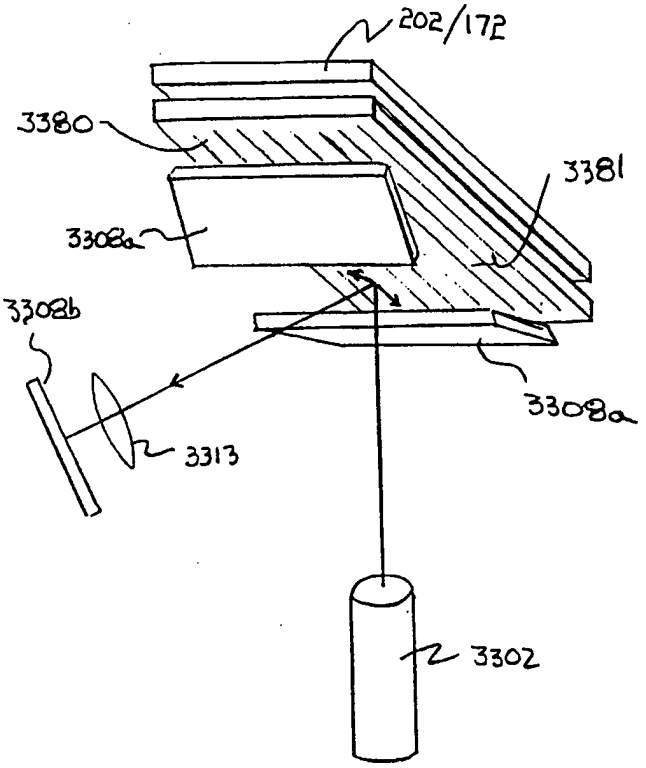


FIG. 34

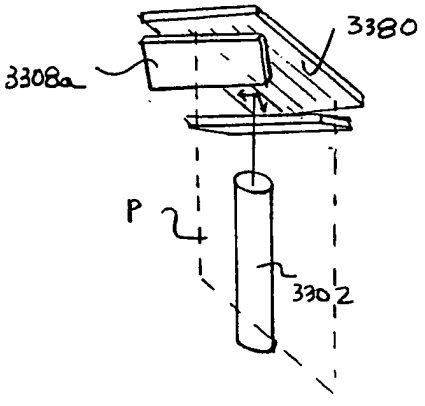


FIG. 35

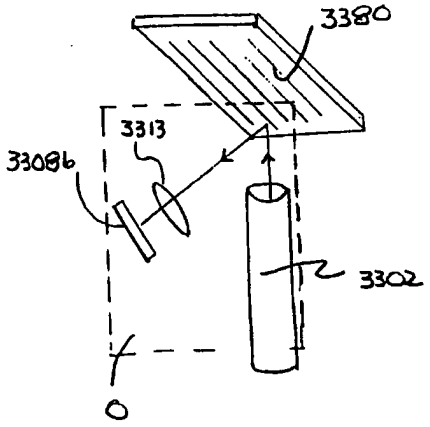


FIG. 36

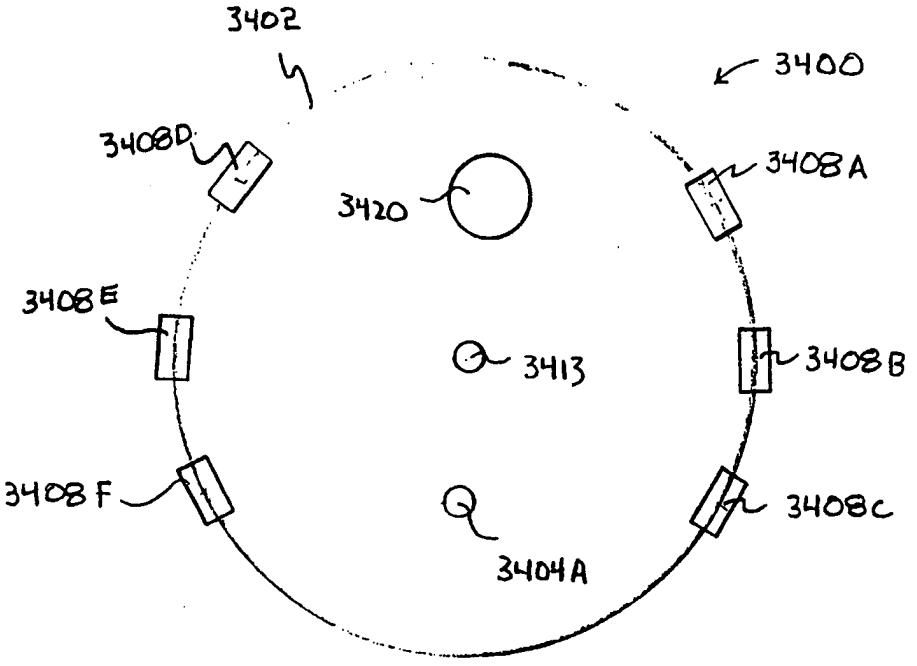

3402
3400
3408D
3408A
3420
3408E
3413
3408B
3408F
3408C
3404A

FIG. 37

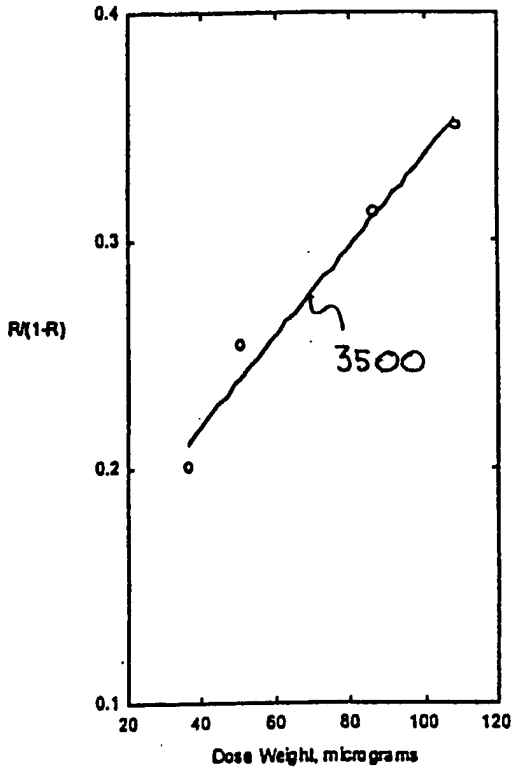

0.4
0.3
0.2
0.1
R/(1-R)
3500
20
40
60
80
100
120
Dose Weight, micrograms

FIG. 38

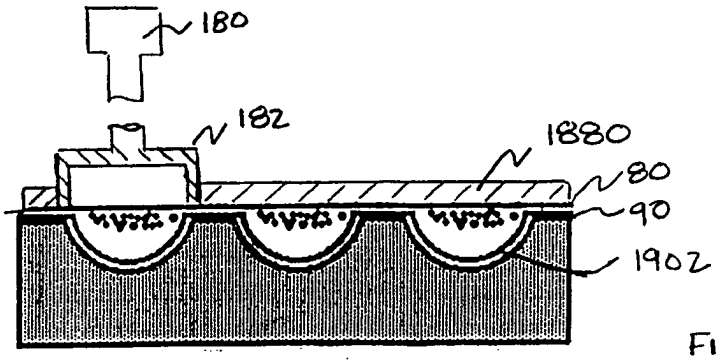

180
182
1880
80
90
1902

FIG. 39

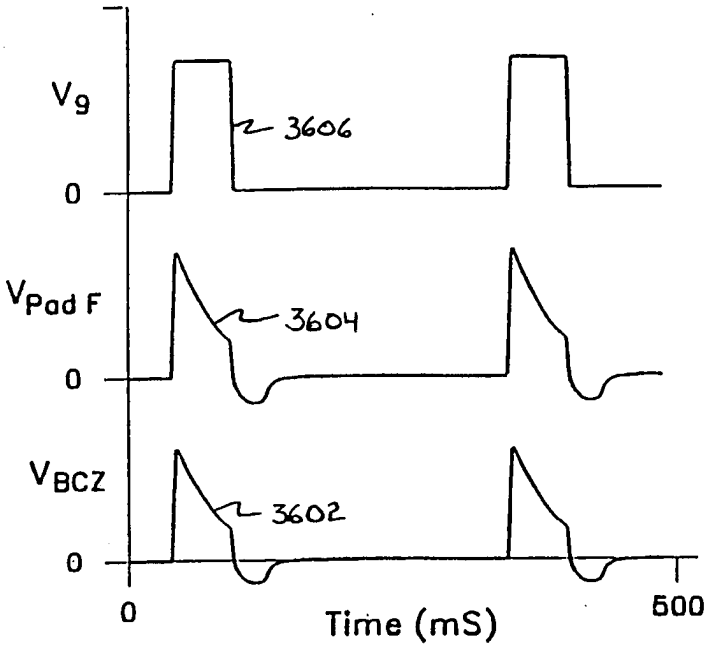
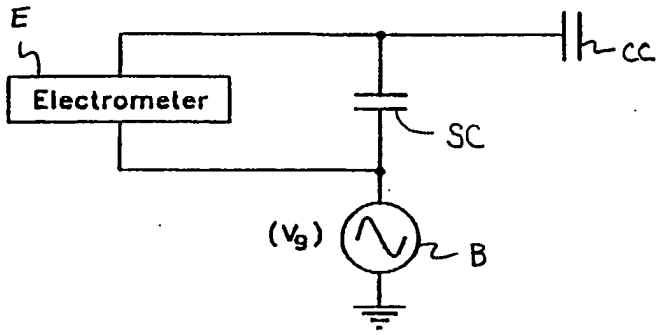

V_g
3606
0
$V_{Pad\ F}$
3604
0
V_{BCZ}
3602
0
0
Time (mS)
500

FIG. 41

FIG. 40



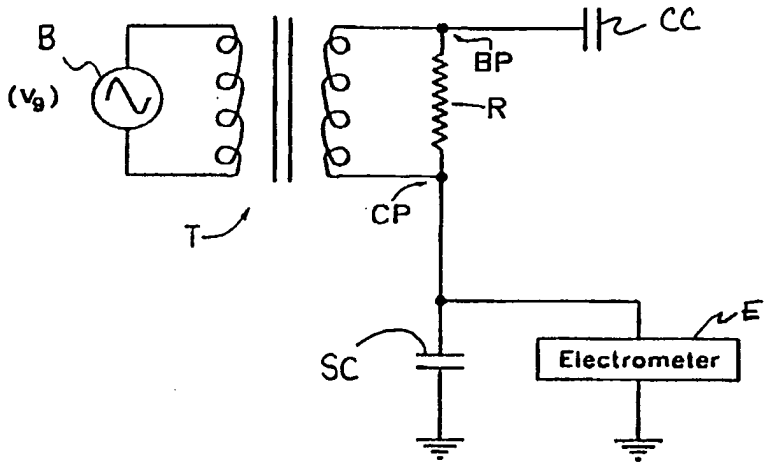


FIG. 42

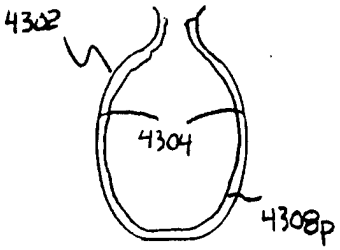


FIG. 43a

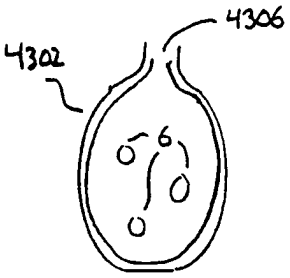


FIG. 43b

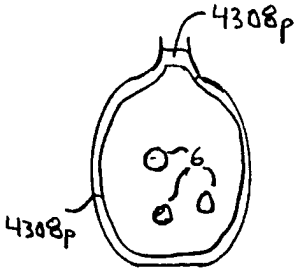


FIG. 43c

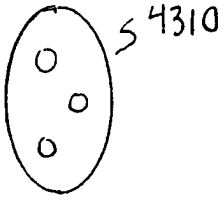


FIG. 43d

FIG. 44a

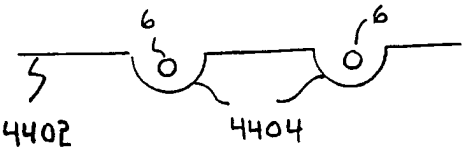




FIG. 44b

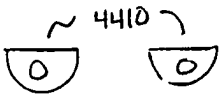


FIG. 44c

FIG. 46

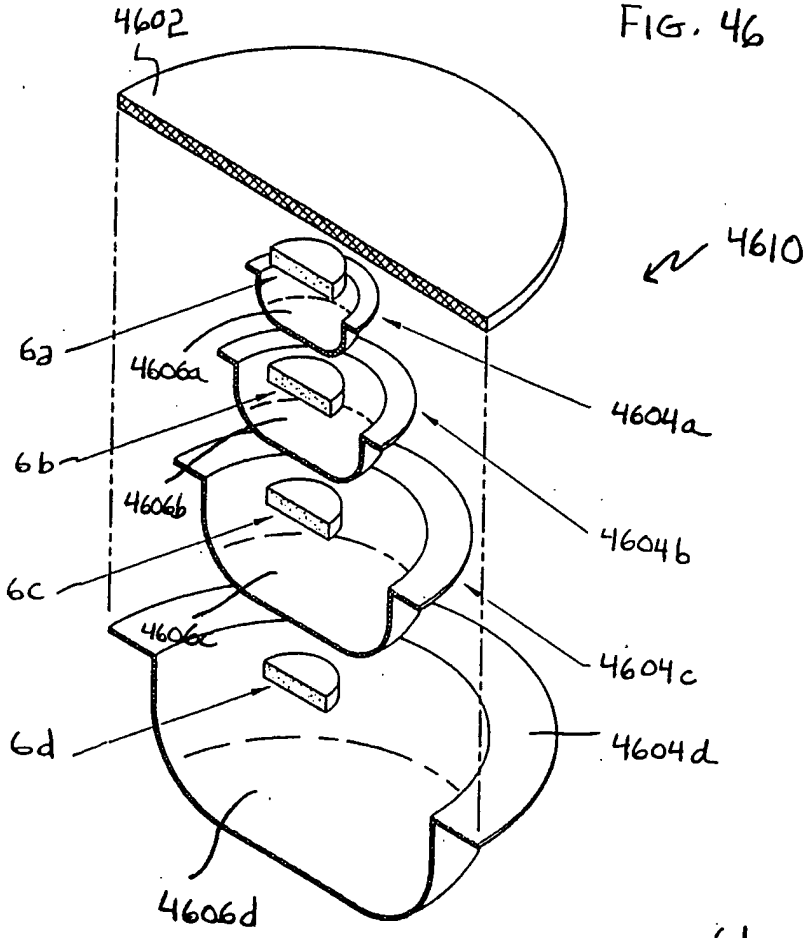
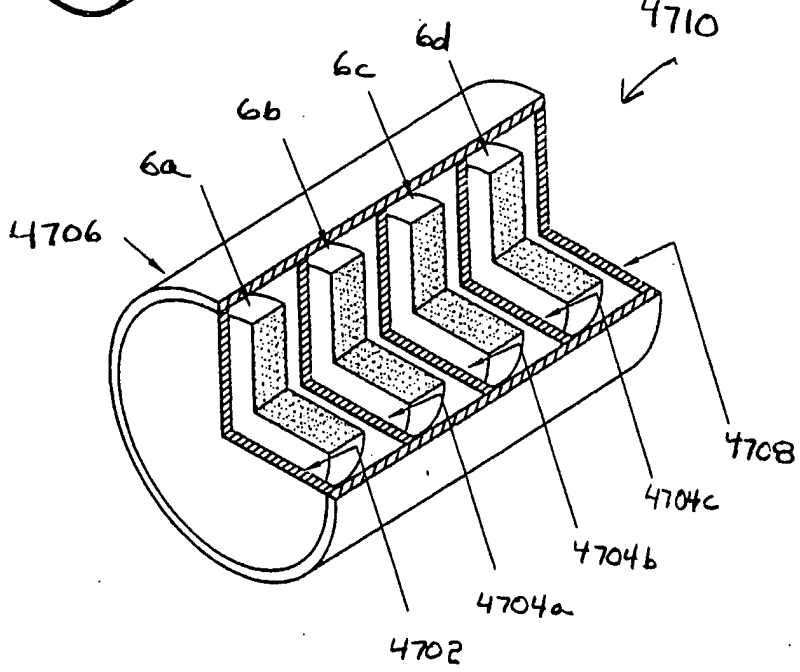

4602
4610
6a
4606a
4604a
6b
4606b
4604b
6c
4606c
4604c
6d
4604d
4606d

FIG. 47


4710
6d
6c
6b
6a
4706
4708
4704c
4704b
4704a
4702

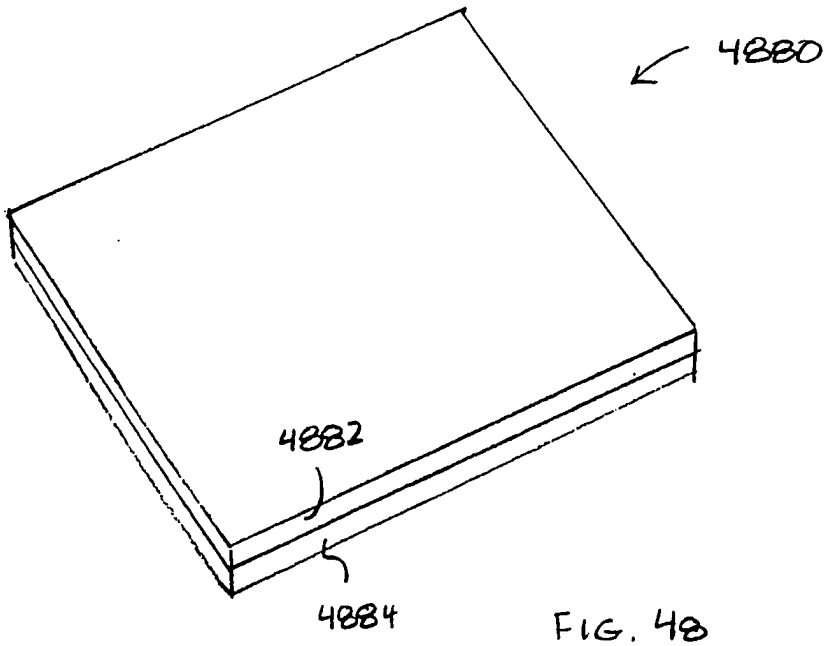
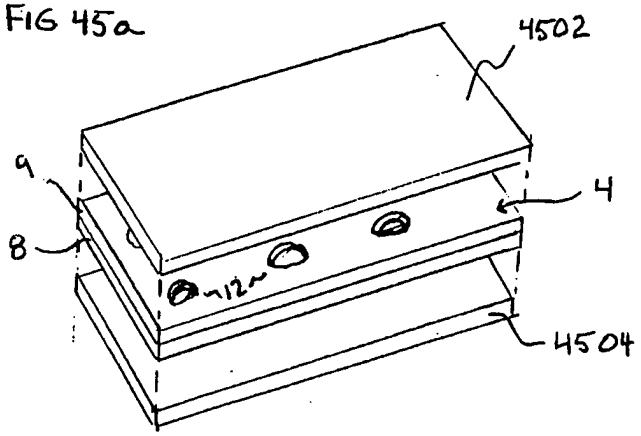
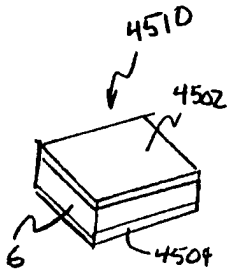


FIG. 48

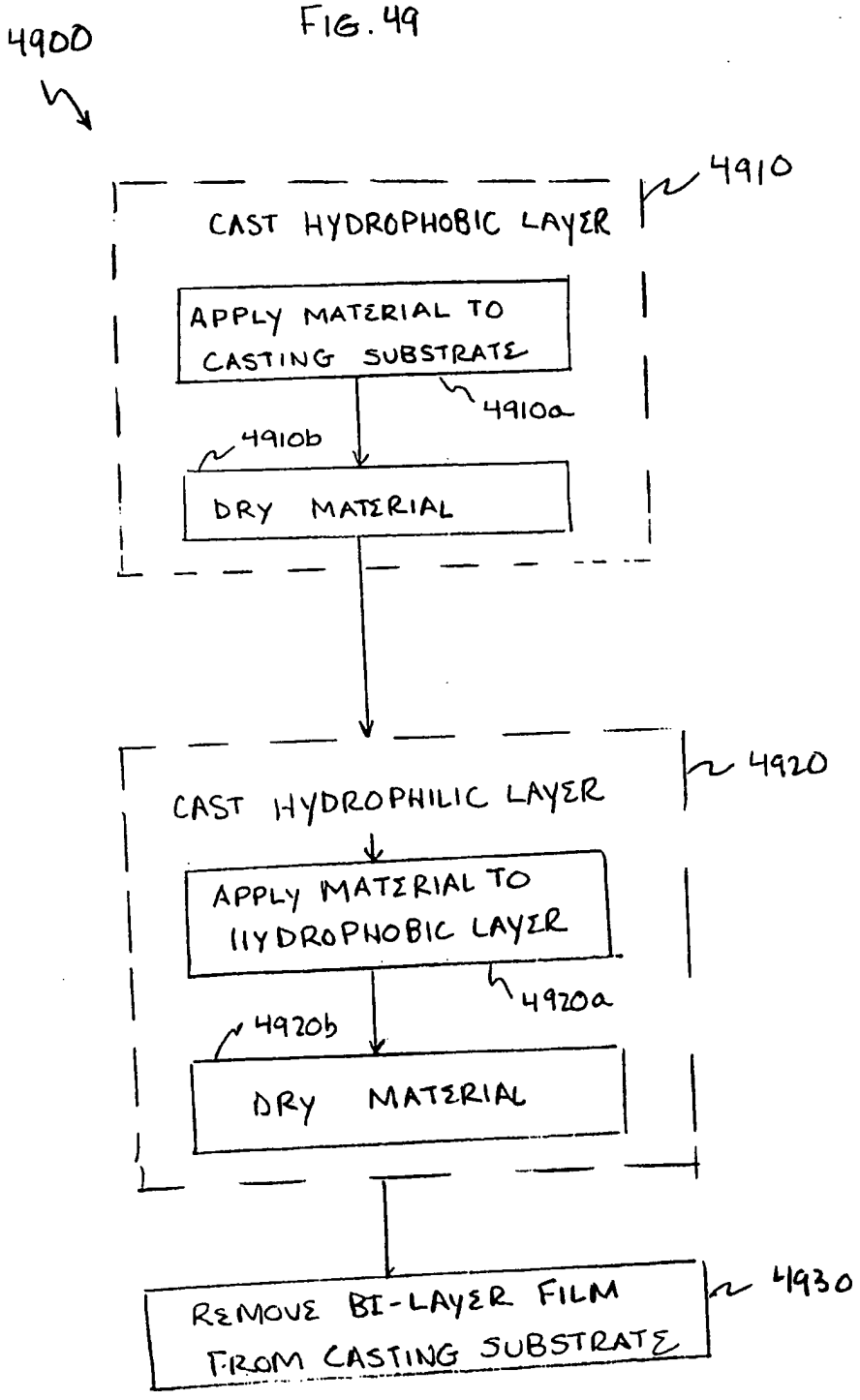
FIG 45a





FIG, 45b

FIG. 49


4900
CAST HYDROPHOBIC LAYER
4910
APPLY MATERIAL TO CASTING SUBSTRATE
4910a
4910b
DRY MATERIAL
CAST HYDROPHILIC LAYER
4920
APPLY MATERIAL TO HYDROPHOBIC LAYER
4920a
4920b
DRY MATERIAL
REMOVE BI-LAYER FILM FROM CASTING SUBSTRATE
4930

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12772

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/70
US CL :118/621, 712; 424/451

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 118/621, 712; 424/451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 4,332,789 A (MLODOZENIEC) 01 June 1982, col. 6, line 7 through col. 7, line 50.	1-76
A	US 4,554,611 A (LEWIN) 19 November 1985, col, 2, line 53 through col. 3, line 68.	1-76

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 AUGUST 1999	21 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES SELLS Telephone No. (703) 308-2090

Form PCT/ISA/210 (second sheet)(July 1992)★